DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date · DEC 20 1995

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Thoratec Laboratories Corporation
Thoratec® Ventricular Assist Device System - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved ✓ Disapproved ____ Date 11-27-96

Prepared by Dina Justice, CDRH, HFZ-450, December 8, 1995, 443-8262

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO._____]

Thoratec Laboratories Corp.; PREMARKET APPROVAL OF Thoratec® Ventricular Assist Device System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Thoratec Laboratories Corp., Berkeley, CA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of Thoratec® Ventricular Assist Device System. After reviewing the recommendation of the Circulatory Systems Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of December 20, 1995, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, rm. 1-23, Rockville, MD 20857.

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FOR FURTHER INFORMATION CONTACT:

Dina A. Justice,

Center for Devices and Radiological Health (HFZ-450),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-443-8262.

SUPPLEMENTARY INFORMATION: On June 26, 1992, Thorâtec Laboratories Corp., Berkeley, CA, 94710, submitted to CDRH an application for premarket approval of Thoratec® Ventricular Assist Device System. The device is a ventricular assist device and is intended as a bridge to cardiac transplantation for use in patients suffering from end-stage heart failure. The patient should meet all of the following criteria: 1) candidate for cardiac transplantation, 2) imminent risk of dying before donor heart procurement, and 3) dependence on, or incomplete response to, continued vasopressor support.

On December 5, 1994, the Circulatory System Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On December 20, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its Approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request.

Opportunity for Administrative Review

Section 515(d)(3) of the act, (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under §10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for

resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Gary Cederwall
c/o Patsy J. Trisler, J.D.
Vice President, Regulatory Affairs
Advanced Bioresearch Associates
1700 Rockville Pike, Suite 535
Rockville, Maryland 20852-1631

DEC 20 1995

Re: P870072
Thoratec® Ventricular Assist Device System
Filed: June 26, 1992
Amended: June 30, October 19, and November 23, 1992; January 21, March 15, July 20, August 25, October 29, October 29, and October 29, 1993; March 10, June 15, July 8, August 16, August 23, August 24, September 26, October 28, November 9, November 9, November 16, November 23, November 30, November 30, December 16, and December 20, 1994; March 16, April 24, April 25, July 20, August 2, September 5, September 25, November 7, November 28, and December 6, 1995

Dear Mr. Cederwall:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Thoratec® Ventricular Assist Device System. This device is intended as a bridge to cardiac transplantation for use in patients suffering from end-stage heart failure. The patient should meet all of the following criteria: 1) candidate for cardiac transplantation, 2) imminent risk of dying before donor heart procurement, and 3) dependence on, or incomplete response to, continued vasopressor support. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

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Expiration dating for this device has been established and approved at 3 years.

FDA recommends that periodic reporting as described in CFR 21 814.84(b) be provided on a quarterly basis.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

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At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

If you have questions concerning this approval order, please contact Dina Justice at (301) 443-8262.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

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CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, 340
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Thoratec® Ventricular Assist Device System

Premarket Approval (PMA) Application P870072

21 CFR §814.20(b)(3)

SUMMARY OF SAFETY AND EFFECTIVENESS

Thoratec Laboratories Corporation

2023 Eighth Street

Berkeley, California 94710-2090

I. GENERAL INFORMATION

Device Generic Name:	Ventricular assist device
Device Trade Name:	Thoratec® Ventricular Assist Device System
Applicant's Name and Address:	Thoratec Laboratories Corporation 2023 Eighth Street Berkeley, California 94710
PMA Application Number:	P870072
Date of Panel Recommendation:	December 5, 1995
Date of Notice of Approval to the Applicant:	December 20, 1995

II. INDICATIONS FOR USE

The Thoratec® Ventricular Assist Device (VAD) is intended as a bridge to cardiac transplantation for use in patients suffering from end-stage heart failure. The patient should meet all of the following:

1. Candidate for cardiac transplantation.
2. Imminent risk of dying before donor heart procurement.
3. Dependence on, or incomplete response to, continued vasopressor support.

III. CONTRAINDICATIONS

None, other than contraindications to cardiac transplantation.

IV. WARNINGS

A. Patient Population

VAD patients with prosthetic aortic valves may have increased risk of thromboembolism due to blood flow shunted away from the valve.

Patients with greater than 1.5+ aortic insufficiency should either not be considered a candidate for VAD support, or should be considered only after repair or replacement of the aortic valve.

Significant right-to-left shunting can occur in patients with a patent foramen ovale. Patency of the foramen ovale should be considered and corrected if necessary, prior to insertion of VADs.

Cannulas may be difficult to insert in patients with small hearts, or in patients with congenital abnormalities, or previous cardiac reconstructive surgery. This issue was not addressed in depth during the clinical study.

Patients with hepatic and/or renal dysfunction may require 2 to 3 weeks of VAD support for major organ function to recover.

Patients with elevated levels in the panel of reactive antibodies (PRA) may require extensive duration of VAD support in order to locate a donor heart. Patients should be excluded if there is not a reasonable expectation of finding a donor heart.

B. Procedural Techniques

The VAD is provided sterile; caution must be taken in opening the package. Do not resterilize. Do not use if package is damaged.

Do not disassemble the VAD. Collet nuts and collets must be removed to attach cannulae to the VAD, and this can be performed by hand. Disassembly or attempts to loosen the cap ring, valve housing nuts, or any other component of the VAD may affect VAD function.

Do not use polar organic solvents, such as ketones, chlorinated hydrocarbons, and aromatic hydrocarbons, anywhere near the VAD. Such use has caused stress-cracking of the polysulfone and other damage to the VAD housing. These solvents include, but are not limited to, acetone, methyl ethyl ketone (MEK), methylene chloride, chloroform, trichloroethane, and benzene and its derivatives.

Do not use povidone-iodine (e.g., betadine) ointments, or other polyethylene glycol-based ointments in contact with the cannula for prophylactic care of the transdermal skin site. Such use over several months has caused cannula degradation at the end of the wire reinforced region. Povidone-iodine solution (not containing polyethylene glycol) is recommended.

V. PRECAUTIONS

A. Training of Personnel

Surgical, nursing, and perfusion staff responsible for the VAD program at each hospital should complete the Thoratec VAD Training program.

B. Technique of VAD Placement

Use strict aseptic techniques during implantation and extreme care throughout VAD support to prevent infection.

The arterial graft on the arterial cannula must be preclotted before use.

Do not cut the tapered end of the atrial cannula.

The distal end of the arterial and ventricular cannulas can be trimmed, but at least 4 cm of nonwire reinforced polyurethane cannula are required for proper attachment to the VAD.

Do not allow tissue fluid or particulate matter to contaminate the inside of the cannulas, especially when passing the cannulas through the percutaneous exit tunnels.

The VAD valve housing has a very sharp edge designed to minimize seam thrombus. Do not dent or scratch the sharp edge, and be careful to avoid cutting yourself.

Do not allow blood or other fluids to contact the electrical fill switch connector on the VAD.

Do not initiate VAD pumping until the blood pump has been completely de-aired after connecting the cannulas.

If VAD cannulas are not properly inserted, suboptimal VAD blood flows may occur.

C. External Alarms

The VOLUME mode is the recommended control mode for most patients. This is the only mode where both audible and visual alarms on the Dual Drive Console (triggering on the absence of the VAD fill signal) are present if the VAD were to cease to operate due to adverse scenarios such as blockage of the pneumatic drive or cannulae. Any patient supported with the VAD drive console in the ASYNC or EXT SYNC modes must have the external alarm output on the drive console connected to the hospital nurse call system, or other similar external alarm system. This alarm output will trigger the external independent alarm after an 8 second absence of the VAD fill signal, thus alerting the user to check the VAD and drive console to determine that they are operating properly. This alarm is available in all control modes, but is not required when using VOLUME mode since internal audible alarms are present in that mode.

D. Required System Backup

Each console contains two independent drive modules, and therefore contains adequate built-in back-up capability for univentricular support. For patients receiving biventricular support, a complete dual drive console must be available as a back-up to be used in the event of a failure of the primary console.

Personnel should be trained how to hand pump a VAD in the event of an drive console failure. If for any reason there is a drive console failure, blood flow can be maintained to the patient and stasis prevented in the blood pump by disconnecting the VAD airline tube from the drive console and connecting it to the hand bulb for the short period of time necessary to connect the back-up drive console. Squeeze the hand bulb about once per second to empty and fill the blood pump. Connect the back-up drive console as soon as possible. This procedure is for emergency use only.

E. Steps to Minimize the Risk of Thrombosis

At low beat rates there is an increased risk of thrombus formation in the VAD. Therefore it is recommended that the device be operated at rates above 40 bpm and with complete filling and ejection of the VAD blood pump in the VOLUME mode. Pneumatic drive ejection pressures of at least 100 mmHg above the patients systolic blood pressure are recommended for complete ejection. Complete VAD emptying can be verified by using a flashlight. During weaning the patient from the VAD, and or during other conditions that result in low flow or beat rates below 40 bpm, continuous infusion of heparin for anticoagulation to achieve a partial thromboplastin time of 1.5 times control is recommended.

F. Interaction with Magnetic Resonance Imaging

This device contains ferro-magnetic metal components. Do not perform MRI imaging procedures on patients with the Thoratec® VAD.

VI. DEVICE DESCRIPTION

A. General Features

The Thoratec® VAD System includes a ventricular assist device designed to support the circulation of blood in the pulmonary and/or systemic circulation when the natural heart, with the help of standard drug therapy and intraaortic balloon counterpulsation, is unable to maintain normal blood flows and pressures in those vascular beds. To accomplish this support, blood is shunted from the natural heart to the VAD, which then pumps pulsatile blood flow back to the body at normal arterial pressures. The goal is to provide sufficient blood flow to maintain major organ function in patients awaiting heart transplantation.

The VAD System can be used in several configurations to provide for the circulation of blood in either or both the pulmonary or systemic vascular beds at physiological pressures and flows (see Figure 1). The system consists of three major components: a blood pump, cannulae, and a drive console.

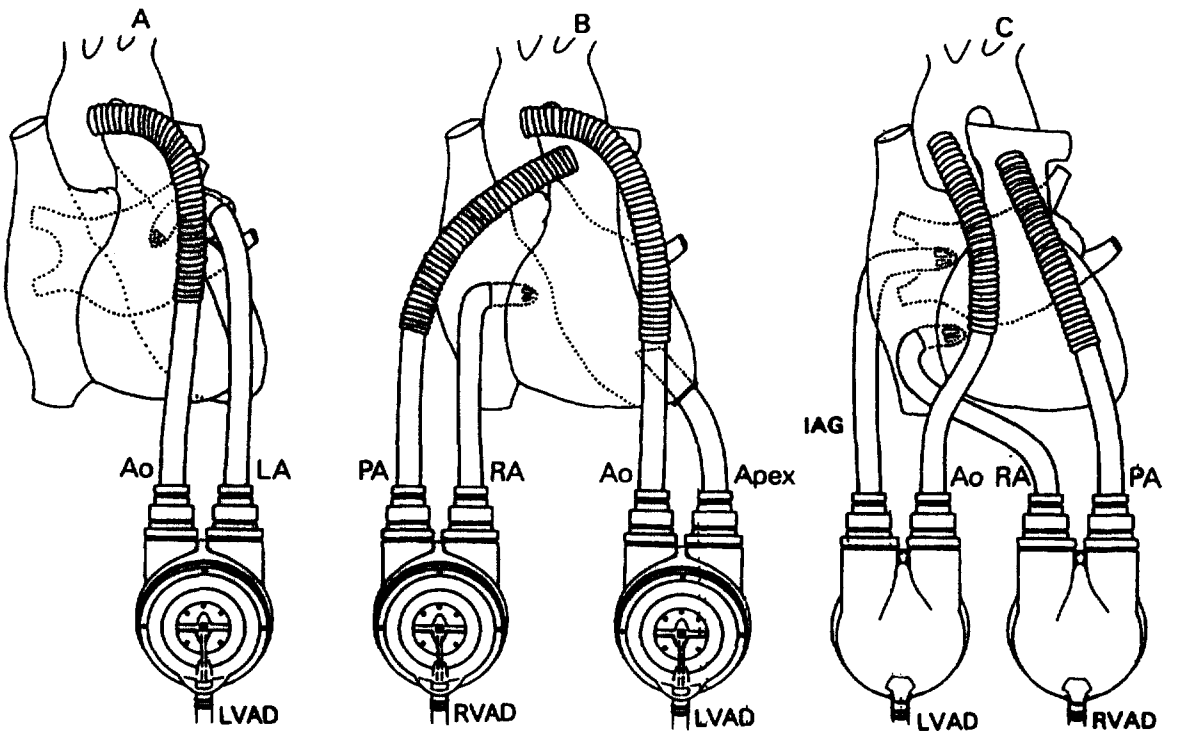


Figure 1. Thoratec®Ventricular Assist Device (VAD) and three cannulation approaches for univentricular left heart support (Panel A), and biventricular support (Panels B and C). L = LVAD, R = RVAD, Ao = aorta, LA = left atrial appendage, PA = pulmonary artery, RA = right atrium, Apex = left ventricular apex, IAG = cannula inserted via the interatrial groove and directed towards LA roof. Note that the VADs in Panel C are turned over and are on the sides of the chest that are opposite of those in Panel B. (Modified from Farrar, DJ et al, New England Journal of Medicine 1988; 318: 333-340. Copyright 1988, Massachusetts Medical Society).

B. Thoratec® VAD Blood Pump

The central part of the system is the blood pump, which can be used as a left (LVAD), right (RVAD), or biventricular (BVAD) assist device. It has a rigid plastic case containing an elastomeric blood pumping sac, composed of Thoratec's polyurethane BPS-215M. The blood sac is compressed by air from a pneumatic drive console to eject blood from the sac. Mechanical valves, mounted in the inflow and outflow ports of the blood pump, control the direction of blood flow. The blood pump has an effective stroke volume of 65 ml and, depending on various conditions, will pump up to 6.5 l/min at a rate of 100 beats per minute.

C. Cannulae

Each VAD blood pump is connected to the patient's heart and great vessels with cannulae. Cannulae can be inserted in the left or right atrium or placed in the left ventricular apex to provide inflow to the VAD blood pump. Blood is returned to the patient with an arterial cannula in the aorta or the pulmonary artery depending on whether the left or right ventricle is being assisted.

D. Thoratec® Dual Drive Console and Accessories

Each VAD blood pump is connected to the patient's heart and great vessels with cannulae. Cannulae can be inserted in the left or right atrium or placed in the left ventricular apex to provide inflow to the VAD blood pump. Blood is returned to the patient with an arterial cannula in the aorta or the pulmonary artery depending on whether the left or right ventricle is being assisted.

E. The VAD blood pump, cannulae, and leads are supplied sterile and non-pyrogenic for single-use only. Do not reuse or resterilize.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional medical therapy, including the use of pharmacologic agents and the intraaortic balloon pump (IABP), are employed to assist in maintaining heart pumping function for patients who have suffered acute heart failure. When the heart fails as a pump, mechanical circulatory support is necessary.

VIII. MARKETING HISTORY

Marketing of the Thoratec® VAD outside the U.S. began in 1983, with introduction of the device in the following countries: Australia, Brazil, Canada, Germany, Italy, Japan, Spain, Switzerland, Taiwan, and the United Kingdom. The VAD System has not been withdrawn from marketing for any reason relating to safety and effectiveness of the device.

IX. ADVERSE EVENTS

Please refer to Table XIII-1 for more detailed information.

Based on the clinical study, the medical risks associated with the use of the VAD include the following critical adverse events (listed in order of decreasing frequency):

- Cardiovascular dysfunction
- Hepatic dysfunction
- Renal dysfunction
- Bleeding
- Hemolysis
- Infection
- Reoperation
- Death
- Thromboembolism

A variety of other adverse events were noted during the study including:

- Mechanical dysfunction
- Thrombocytopenia
- Neurological dysfunction
- Respiratory dysfunction
- Pleural effusions
- Pancreatitis

Note:

The need for reoperation may result from excessive bleeding, right ventricular failure requiring RVAD insertion, VAD inflow problems requiring cannula repositioning, etc.

Neurological dysfunction may result from pre-existing hypoxic brain injury (for example, from pre-VAD cardiac arrest or hypotension), or events during the VAD period such as cerebral hemorrhage, drug-related side effects, and cerebral hypoperfusion.

Embolism may result in stroke, pulmonary or other non-cerebral organ infarction, leg ischemia, or other vascular obstruction.

In addition, it is possible that the VAD will produce no significant hemodynamic improvement.

The VAD should not be resterilized by user.

X. NON-CLINICAL LABORATORY STUDIES

A. Biocompatibility

The blood contacting polyurethane, BPS-215M has been tested in accordance with the *Tripartite Biocompatibility Guidance for Medical Devices*. Those results are summarized below in Table X-1:

Table X-1
BPS-215M Biocompatibility Testing

Test Performed	Result
Irritation Test	No skin reactions
Sensitization	Mild
Cytoxicity	Non-toxic
Acute Systemic Toxicity	Non-toxic
Hemocompatibility	Non-thrombogenic
Intramuscular Implantation (7 days)	Passed
Ames Mutagenicity	Non-mutagenic
Subchronic Toxicity (60 day intramuscular implantation)	Passed

B. In-vitro Characterization Studies

In vitro characterization of VADs on a mock circulatory loop demonstrates the VAD's ability under nominal operating conditions (mean arterial pressure of 90 mmHg, filling pressures of 10 mmHg, a drive pressure of 220 mmHg and a vacuum of -30 mmHg) to pump 4.36 l/min using atrial cannulation and 5.45 l/min using ventricular cannulation, which is sufficient to support the systemic or pulmonary circulation.

C. In-vivo Animal Testing

An animal study of 30 days duration was conducted in which eight calves were implanted with the Thoratec® VAD. The purpose of the study was to evaluate the VAD's effects on healthy animals by assessing hemodynamics, damage to platelets and red cells, hepatic function, renal function, infection, and post-mortem pathological data. The hemodynamic results showed the VAD to be effective in pumping an average of 5.5 l/min during the test period with no major complications. The values for plasma hemoglobin, hemoglobin, platelet count, total bilirubin, blood urea nitrogen, white cell count and fibrinogen were within the normal laboratory range throughout the test, and demonstrated acceptable function and effect on host organs. Autopsy reports demonstrated some degree of renal infarction, described as slight to moderate. Gross examination of the explanted VADs showed the blood sacs to be free of thrombi.

D. Shelf Life and Sterilization

The sterile, disposable components of the Thoratec® VAD system (VADs, cannulae, pneumatic leads, and electrical leads) have been tested to establish a three year shelf life. The devices were packaged in their final packaging configuration and subjected to three (3) production EtO sterilization cycles, the maximum number validated. After packaging and sterilization, devices were subjected to simulated adverse shipping temperatures, accelerated shelf life aging of up to 188 days (equivalent to three years of real-time shelf life), simulated adverse shipping and handling (per National Safe Transit Association Preshipment Test Procedures), and microbial barrier testing by dust chamber challenge.

The results of the shipping and shelf life testing demonstrate that:

1) VAD components remain sterile following multiple sterilizations, simulated shipping stress, and three years of shelf life. All microbial targets from all product packages tested negative, negative controls all tested negative, and positive controls tested positive.

2) Sterile barrier characteristics of VAD packaging remain effective following multiple sterilizations, simulated shipping stress, and three years accelerated shelf life. All samples met the acceptance criteria for the force required to peel the Tyvek® lids from the package trays and peel-pouches.

3) VAD, cannula, and electrical lead functionality have been demonstrated following multiple sterilizations, simulated shipping stress, and three years of shelf life.

4) No physico-chemical or biocompatibility changes have occurred to the blood contacting material, BPS-215M, following multiple sterilizations and three years of shelf life. No changes in the FT-IR spectra were found, and no free amines were found. All samples were found to be non-cytotoxic.

XI. RELIABILITY

A. Overview

A total of eight VADs were tested on a mock circulatory loop for six months. Four VADs were electively removed from testing for analysis; the actuation and switch diaphragms, valves, and cannula connectors of these four VADs were analyzed for wear and durability, and the blood sacs were tested for leakage. Reliability testing was also conducted on four dual drive consoles with eight complete VAD drive modules and there were no major failures.

Based on the in-vitro overall system reliability testing (through the study cut-off date), there is a 94% chance (using the lower 90% confidence intervals) that this device will be free of critical failures through 50 days of use, and a 65% chance that this device will be free of critical failures through one year of use.

B. Results

Table XI-1 presents the overall reliability for the Thoratec® VAD which represents the data from complete system and component testing discussed above. Table XI-2 presents the reliability of the component testing. Reliability (R) is presented at 50 days and at 365 days.

Table XI-1

Thoratec VAD Overall System Reliability (@ lower 90% confidence interval)	
$R_{50\ days}$	0.94
$R_{365\ days}$	0.65
Total Test Time[1]: 3,319 days	

Table XI-2

Thoratec VAD In-Vitro Reliability Test Results (@ lower 90% confidence interval)			
	Blood Pump Test Data	**Drive Module Test Data**	**System Life Test Data**
Total Test Time[1] (days)	3,319	3,676	3,319
$R_{50\ days}$	0.94	0.97	0.91
$R_{365\ days}$	0.65	0.80	0.52

[1]Through the study cut-off date (July 1, 1994).

Four VADs remain on life test, and as of July 1, 1994, and all four have reached 606 to 661 days of pumping without failure. The results of VAD testing establish that with 90% confidence, the VAD blood pump reliability for 30, 40, 50, and 365 days of pumping is 97%, 96%, 94%, and 65%, respectively.

In addition, the wear of the actuation diaphragm and switch diaphragm is well within acceptable limits, and there is no significant wear on the inflow or outflow valves.

XII. DESCRIPTION OF CLINICAL STUDIES

A. Abstract

The purpose of the study was to evaluate patients who had VADs placed prior to heart transplantation to maintain patient viability while waiting for a donor heart. Patients (ages 15-60 years) were selected who were awaiting heart transplantation and at imminent risk of death before a donor heart could be obtained. Qualifying patients [i.e., patients who met all of the study entrance criteria (Cohort 1A)] had received maximal conventional therapy, had pulmonary capillary wedge pressure ≥ 20 mmHg and either a cardiac index ≤ 1.8 L/min/m^2 or systolic pressure ≤ 90 mmHg or mean pressure ≤ 70 mmHg. Patients were excluded for total bilirubin ≥ 5 mg/dl or creatinine ≥ 4 mg/dl or irreversible end organ dysfunction. Seventy-one patients (54 males, 17 females) met all inclusion/exclusion criteria. The gender distribution (24% female) was consistent with the UNOS registry of patients awaiting cardiac transplantation (17.5% female). A retrospective control group (9 males, 1 female) met all the inclusion/exclusion criteria but were not treated with the ventricular assist system.

Results: Forty-nine of the 71 (69%) of the patients received biventricular (BVAD) support; 22 (31%) received only left ventricular (LVAD) support. Thirty-two patients required a total of 51 reoperations; 35 for bleeding; 16 for other reasons. Preoperative cardiac index (1.4 ± 0.7 ℓ/min/m^2) improved following VAD placement to an LVAD flow index of 2.5 ± 0.5 L/min/m^2 on post-VAD day 1 ($p < 0.001$) and remained within a clinically normal range thereafter. (At two weeks of support, LVAD flow index averaged 2.8±0.5 L/min/m^2.) Median VAD support period was 16 days (mean: 35 days, maximum: 247 days). The median survival time from implant to follow-up cut-off date (June 1, 1994) was 223 days (mean: 503 days), with 38 current survivors. Median survival time was 10 days (mean: 14 days) in 10 control patients with 0 survivors. Of the 71 patients implanted with the device, 49 (69%) survived to receive a transplant compared to 0 of 10 control patients. Twenty-six of 55 (47%) patients implanted with the device survived at least 1 year post transplantation, and the other sixteen patients remained alive but had not yet reached the one-year period as of the study cut-off date (June 1, 1994). The Kaplan-Meier estimate of survival for the 49 transplanted patients was 84% at 1 year. Multivariate analysis identified two correlates of successful bridge to transplantation: low preoperative total bilirubin levels and absence of previous cardiac operations.

B. Subject Inclusion and Exclusion Criteria

The 71 patients in Thoratec's Cohort 1A were enrolled in 21 institutions in the United States under the Bridge to Transplantation IDE. The subject inclusion criteria basically defined an acceptable heart transplant candidate, between the ages of 15 and 60, of either sex, who was in imminent risk of dying if no donor heart was procured, in spite of appropriate medical and pharmacologic management. The bridge-to-transplant protocol also specified that a patient meet hemodynamic entry guidelines as follows:

1. Mean left atrial pressure (or pulmonary capillary wedge pressure) is greater than or equal to 20 mmHg, and either,
   a. Cardiac index is less than or equal to 1.8 L/min/m^2, or
   b. Peak systolic arterial pressure is less than or equal to 90 mmHg, or mean arterial pressure is less than or equal to 70 mmHg,

   or
2. The patient has a cardiac arrest or is in ventricular fibrillation and cannot be converted.

The exclusion criteria were the usual contraindications to heart transplantation.

C. Study Population

The Cohort 1A group of patients consisted of 54 males and 17 females with an average age of 43 years (range: 17 to 60). The average body weight was 73 kg (range: 40 to 126 kg) and the average body surface area (BSA) was 1.88 m^2 (range: 1.28 to 2.55 m^2). Thirty-one patients were diagnosed with coronary artery disease (acute myocardial infarction in 5; ischemic cardiomyopathy in 21). Twenty-nine patients were diagnosed with dilated cardiomyopathies, 5 with post-transplant failure, and 6 had other diagnoses. The distributions among the other cohorts was similar. Please refer to Table XII-1 for the baseline demographics and clinical characteristics of these 71 patients, Table XII-2 for baseline hemodynamics, and Table XII-3 for baseline hematology and blood chemistry.

D. Criteria for BVAD Placement

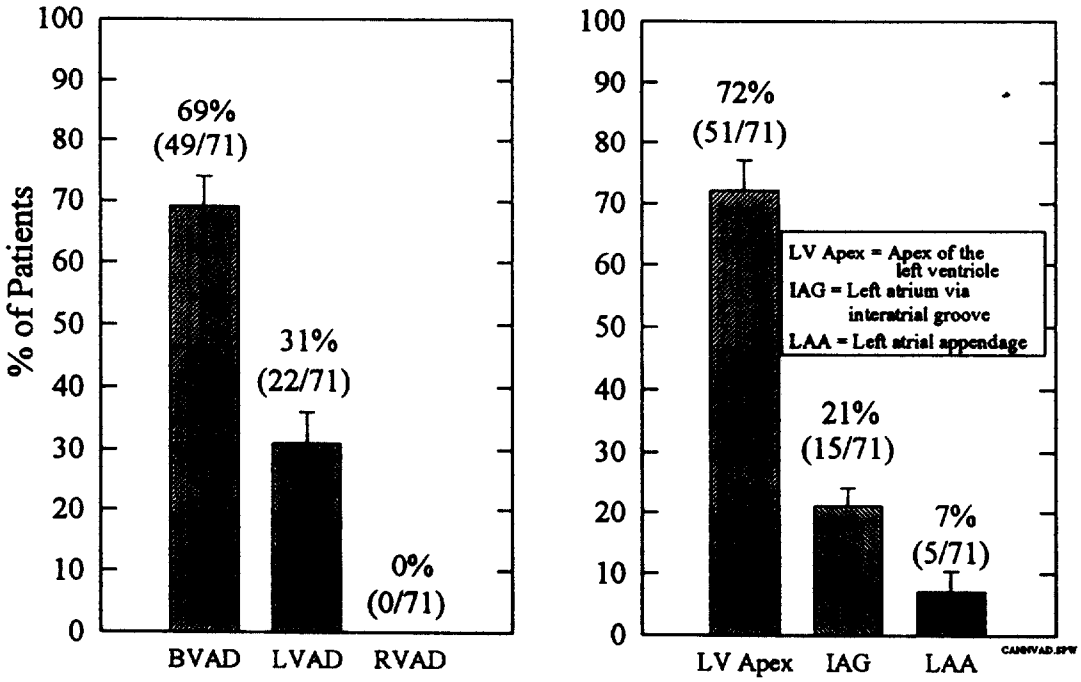
Adequate right ventricular function is essential for the successful utilization of left ventricular assist devices, to provide sufficient blood flow through the pulmonary circulation to the left side of the heart. In situations where there were no accurate physiologic markers of right heart failure, an LVAD was often implanted first. Then a right ventricular assist device was used in addition to a left ventricular assist device (biventricular assist) when right heart failure prevented adequate function of the LVAD, generally when the blood flow index was less than 2.0 ℓ/min/m^2 with a central venous pressure greater than 20 mmHg. Biventricular support was also used in patients with potentially lethal arrhythmias, or severe right ventricular infarction which might have resulted in death during univentricular support. In some patients an RVAD was implanted initially with the LVAD to obviate the need for a reoperation to implant the RVAD.

Outside of the primary data cohort, several patients with isolated right heart failure required an isolated right ventricular assist device.

E. VAD Placement and Cannulation Sites

As shown in Figure XII-1 below, 49 (of 71) Cohort 1A patients received biventricular (LVAD and RVAD) support; the remaining 22 patients received only left ventricular (LVAD) support. The RVAD inflow cannulae were always placed in the right atrium; the outflow cannulae were always attached to the pulmonary artery. LVAD outflow cannulae were always attached to the ascending aorta. LVAD inflow cannulae were placed as indicated in Figure XII-1 shown below.

Figure XII-1. Frequencies of BVAD, LVAD, RVAD and location of LVAD inflow cannulation, Cohort 1A (n=71).



SITE	BVAD	LVAD	RVAD	OVERALL
Left ventricular apex	32 (65%)	19 (86%)	-	51 (72%)
Interatrial groove	13 (27%)	2 (9%)	-	15 (21%)
Left atrial appendage	4 (8%)	1 (5%)	-	5 (7%)
Total VAD patients	49 (69%)	22 (31%)	0	71

XIII. RESULTS

A. Survival

Of the 71 patients implanted with the device, 49 (69%) survived to receive a transplant and 45 of the 49 (90%) were discharged alive. The Kaplan-Meier estimate of survival for the 49 transplanted patients was 84% at 1 year.

Cumulative frequency distributions for days of VAD support are shown in Figure XIII-1. The median VAD support period was 16 days (mean: 35 days, maximum: 247 days). Cumulative survival probability (Kaplan-Meier plots) is shown in Figures XIII-2 and XIII-3 for post-VAD implant and post-transplant survival.

B. Effectiveness

Preoperative cardiac index (1.4 ± 0.7 L/min/m^2) improved following VAD placement to an LVAD flow index of 2.5 ± 0.5 L/min/m^2 on post-VAD day 1 ($p < 0.001$) and remained within a clinically normal range thereafter. (At two weeks of VAD support, LVAD flow index averaged 2.8 ± 0.5 L/min/m^2.)

Hemodynamic parameters are presented in Figures XIII-4 to XIII-6 for LVAD flow index, arterial pressures, and atrial pressures.

C. Safety

Adverse events were collected for all 71 Cohort 1A patients enrolled in the study. The major risks associated with the use of ventricular assist devices are bleeding, infection, renal and hepatic dysfunction, hemolysis, thromboembolism, and reoperation.

Bleeding frequently occurred after VAD implantation, and it can be due to surgical- and device-related reasons at the cannulation sites or arterial anastomoses, or it can occur due to coagulopathy. Fifty-one percent of the patients in this study had excessive post-operative bleeding, and reoperations to control bleeding were required in 31% of the patients, mostly in the first two post-operative days.

There was evidence that the VAD produces some hemolysis, with plasma free hemoglobin after 2 weeks of pumping averaging = 18 ± 9 mg/dL. Blood transfusions may be required for patients who have excessive bleeding or hemolysis.

Infection can also occur at the cannulation sites, around the monitoring lines, or in the blood, urinary tract, or respiratory tract. There was no apparent pattern of organisms or source. Infections (documented by at least one positive culture of blood, urine, sputum, or wound) occurred in 49% of patients. Sepsis was a cause of death in 7% of all patients implanted with VADs.

Fifty-six percent of the patients in this study had evidence of hepatic dysfunction, and 54% showed renal dysfunction during VAD support. In some patients, 2 to 4 weeks of VAD support were required for recovery of these vital organs. Hemodialysis was required in 15% of VAD patients.

Thromboembolism can also occur from the VAD, cannulas, natural heart chambers, or arteries. Embolic stroke occurred in 6 VAD patients (8% of the total). Continuous anticoagulation with heparin or warfarin is recommended.

The incidence of nine critical adverse events during the period of VAD support in the clinical trial is presented in Table XIII-1. These events were recorded using all-encompassing definitions unique to this study, and therefore, comparisons with other devices and/or studies are not appropriate.

Table XIII-1. Critical adverse events by category, while on VAD support, Cohort 1A, n=71.

EVENT CATEGORY	TOTAL		
	# Events	# Pts	% Pts
Cardiovascular dysfunction (e.g. any single event of hypo- or hypertension, arrhythmias, RV failure)	90	55	77%
Hepatic dysfunction (e.g. any single total bilirubin >3× high normal, cholecystitis)	40	40	56%
Renal dysfunction (e.g. dialysis, any single creatinine >1.5× high normal)	38	38	54%
Bleeding (e.g. excessive CT drainage, DIC, tamponade, hematuria)	54	36	51%
Hemolysis (e.g. any single plasma free hemoglobin >3× high normal after 24 hr)	36	36	51%
Infection (e.g. any positive culture, purulent discharge)	50	35	49%
Reoperation (for any cause - e.g. hemostasis, cannula reposition, tracheostomy, cholecystectomy)	51	32	45%
Death	22	22	31%
Thromboembolism (e.g. all autopsy evidence of any organ infarction; stroke, TIA)	27	20	28%

Laboratory parameters indicative of the effect of the device on the body are presented in Figures XIII-7 to XIII-10 for total bilirubin, blood urea nitrogen, creatinine, and plasma free hemoglobin.

D. Evaluation of Gender Bias

The gender distribution of Cohort 1A was 76% male and 24% female. The gender distribution of the control group was 90% male and 10% female. The male predominance is similar to the 82.5% male predominance for cardiac transplant candidates registered with UNOS, the National Organ Procurement and Transplantation Network (1993 Registry).

Gender was not a significant factor associated with any measure of survival. Seventy-one percent (12/17) of the females and 69% (37/54) of the males received cardiac transplants. Eighty-three percent (10/12) of the females and 92% (34/37) of the males who received cardiac transplants were discharged from the hospital. Seventy-three percent (8/11) of the females and 82% (18/22) of the males who were transplanted were alive one year after transplantation.

E. Conclusions Drawn From the Studies

The results presented demonstrate that the Thoratec® Ventricular Assist Device System performed reliably during the VAD study; that the device is biocompatible, sterile, and non-pyrogenic. These results support the conclusion that the Thoratec® VAD is safe for human use.

The clinical study further provided reasonable assurance that the device performs effectively as a bridge to transplantation in a patient who is at imminent risk of dying before donor heart procurement. The data acquired during this multi-center study show that the Thoratec® VAD device is effective in restoring and maintaining patient hemodynamics, and is effective in improving the survival rate for patients awaiting heart transplantation. Post-transplant survival for VAD patients was comparable to patients treated with conventional therapy without VAD support. Furthermore, analysis of the data in relation to gender shows that the Thoratec® VAD is equally effective as a bridge to transplantation in both males and females.

The clinical study showed a high rate of complications (adverse events) with the use of the Thoratec® VAD, as noted for similar critically ill patient populations.

These data, in addition to the quality of life assessments made at one year post-transplantation, demonstrate that in the selected patient population, the benefits of use of the Thoratec® VAD System outweighed the risks, and further, that it is reasonably safe and effective when used for a bridge to transplantation population for the purpose of providing circulatory support for patients who are at imminent risk of dying before donor heart procurement.

XIV. PANEL RECOMMENDATION

On December 5, 1994, the Circulatory System Devices Panel, an FDA advisory panel reviewed and unanimously recommended approval of the application with conditions.

XV. FDA DECISION

FDA completed an inspection of Thoratec's manufacturing facilities (Berkeley, CA) and determined that the manufacturer was in compliance with the Device Good Manufacturing Practices regulation (21 CFR Part 820).

The FDA concurred with the recommendations of the Panel and recommended additional engineering modifications. The sponsor adequately provided the information requested by both the Panel and the FDA.

XVI. APPROVAL SPECIFICATIONS

FDA approval is subject to the sponsor's compliance with the "Conditions of Approval", and that the sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food , Drug, and Cosmetic Act (the act) under the authority section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the

device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in the order (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Thoratec® is required to conduct a postmarket surveillance study of the Thoratec® Ventricular Assist Device System as required by the Safe Medical Devices Act of 1990.

TABLES AND FIGURES

Table XII-1. Baseline Demographic and Clinical Characteristics - mean ± s.d. (range)

	COHORT 1A (n=71)	CONTROLS (n=10)	p- value
Age (years)	43.0 ± 13.0 (17-60)	40.6 ± 14.8 (20-58)	0.5558[1]
BSA (m^2)	1.88 ± 0.23 (1.28-2.55)	2.05 ± 0.31 (1.60-2.45)	0.1489[1]
Weight (kg)	73.4 ± 16.9 (40-126)	87.6 ± 25.2 (55-129)	0.1552[1]
Height (cm)	173 ± 16.5 (73-196)	180 ± 6.4 (165-188)	0.0912[1]
Sex: Male	54 (76%)	9 (90%)	0.4442[2]
Female	17 (24%)	1 (10%)	
Diagnoses:			0.4998[2,3]
Ischemic	31 (44%)	6 (60%)	
AMI	5 (7%)	1 (10%)	
Chronic	26 (37%)	5 (50%)	
Non-ischemic	40 (56%)	4 (40%)	
IDCM	22 (31%)	3 (30%)	
PPCM	3 (4%)	0 (0%)	
VCM	4 (6%)	0 (0%)	
TXF	5 (7%)	1 (10%)	
Other	6 (9%)	0 (0%)	
Original Operation[4]	2 (3%)	0 (0%)	1.0000[2]
Previous Operation[5]	20 (28%)	5 (50%)	0.2705[2]
NYHA[6] Class: I	1 (1%)	0 (0%)	
II	3 (4%)	0 (0%)	
III	4 (6%)	1 (11%)	
IV	62 (89%)	8 (89%)	
Mechanical Ventilation	33 (47%)	3 (30%)	0.4994[2]
IABP	44 (62%)	8 (80%)	0.3180[2]
LV Ejection Fraction (%)	15 ± 4.6 (0-25) n=54	18 ± 6.3 (9-26) n=7	0.1470[1]
Cardiac Arrest	29 (41%)	4 (40%)	1.0000[2]
Emergent Implant	15 (21%)	NA	---
CNS Status: Alert	48 (68%)	8 (80%)	0.7160[2]

[1]Mann-Whitney U test
[2]Fisher Exact test
[3]Ischemic vs. non-ischemic
[4]Operation immediately prior to VAD implant
[5]Previous cardiac operation in patient's history
[6]NYHA Class upon admission

Table XII-2. Baseline Hemodynamics
mean ± s.d. (range)

	COHORT 1A (N=71)	CONTROLS (N=10)	p-values[1]
Cardiac Index ($L/min/m^2$)	1.39 ± 0.67 (0-2.69) n=67	1.12 ± 0.66 (0.0 - 1.7) n=9	0.1054
LAP or PCWP (mm Hg)	29.3 ± 7.6 (20-50) n=61	34.3 ± 9.4 (22 - 48) n=8	0.1704
RAP (mm Hg)	18.4 ± 7.7 (3-32) n=56	20.0 ± 6.5 (8-28) n=8	0.5623
MAP (mm Hg)	63.7 ± 11.4 (35 - 107) n=42	68.0 ± 15.5 (47 - 98) n=8	0.3539
SAP (mm Hg)	80.5 ± 13.5 (50-115) n=49	87.0 ± 16.3 (60 - 118) n=8	0.2443
PAP (mm Hg)	38.2 ± 11.0 (21-65) n=47	----	----

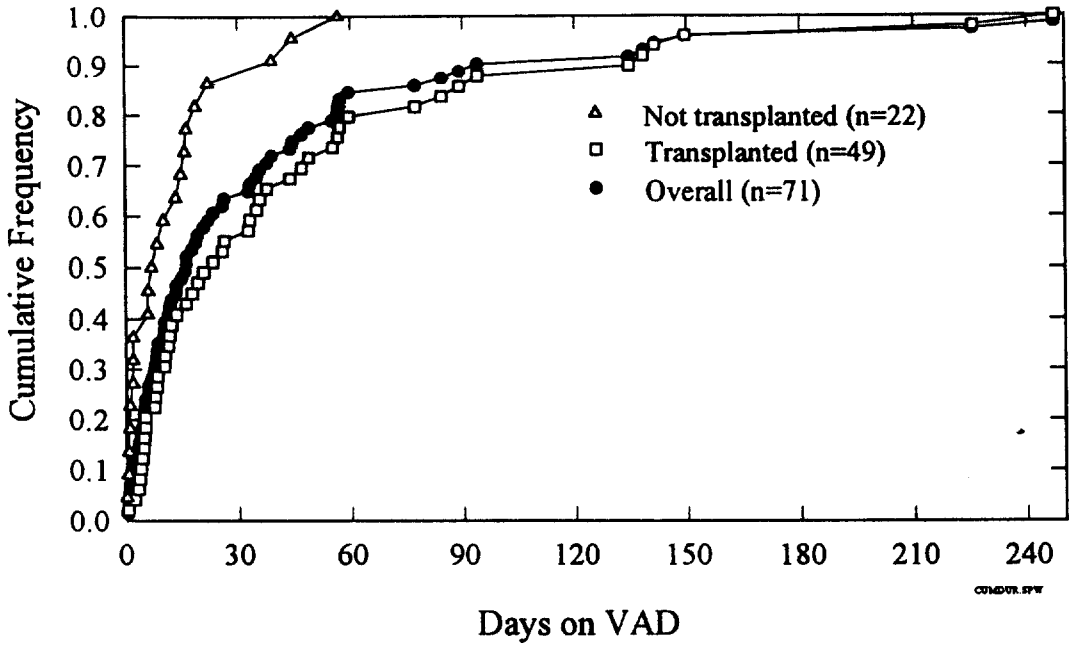
[1] Mann-Whitney U Test

Table XII-3. Baseline Hematology and Blood Chemistry
mean ± s.d. (range)

	COHORT 1A (N=71)	CONTROLS (N=10)	p-values[1]
Creatinine (mg/dl)	1.5 ± 0.6 (0.5-3.5) n=69	1.8 ± 0.8 (0.8 - 3.1) n=10	0.3149
Blood Urea Nitrogen BUN (mg/dl)	32.4 ± 16.4 (7-83) n=69	42 ± 30 (8 - 96) n=10	0.6635
Total Bilirubin (mg/dl)	1.6 ± 1.0 (0.1-4.2) n=64	2.2 ± 1.0 (0.4 - 3.7) n=10	0.0652
Lactic Dehydrogenase LDH (I.U.)	849 ± 1143 (73-5490) n=55	394 ± 446 (64 - 1619) n=10	0.0763
Serum Glutamic Oxaloacetic Transaminase SGOT (I.U.)	270 ± 936 (16-5840) n=63	157 ± 288 (27 - 965) n=10	0.7362
Plasma Free Hemoglobin (mg/dl)	11.7 ± 11.3 (1.0-46.2) n=19	----	----
Fibrinogen (mg/dl)	384 ± 138 (105-665) n=40	292 ± 172 (186 - 490) n=3	0.4314
Fibrin Split Products FSP (mg/dl)	20.4 ± 18.4 (1.4-64.0) n=15	----	----
White Cell Count (1000s/mm^3)	13.6 ± 6.3 (5.3-39.6) n=66	9.8 ± 3.7 (5.1 - 16.0) n=10	0.0528
Hematocrit (%)	33.2 ± 5.9 (15.0-46.4) n=66	35.8 ± 6.9 (28.4 - 48.3) n=10	0.3485
Platelet Count (1000s/mm^3)	200 ± 140 (17-871) n=66	204 ± 88 (113 - 338) n=10	0.7353
Prothrombin Time PT (sec)	15.8 ± 4.4 (10.3-33) n=66	15.1 ± 2.1 (12.0 - 18.3) n=8	0.8755
Partial Thromboplastin Time PTT (sec)	50.8 ± 32.1 (10.7-200) n=64	38.5 ± 11.5 (28.8 - 60.7) n=7	0.3397

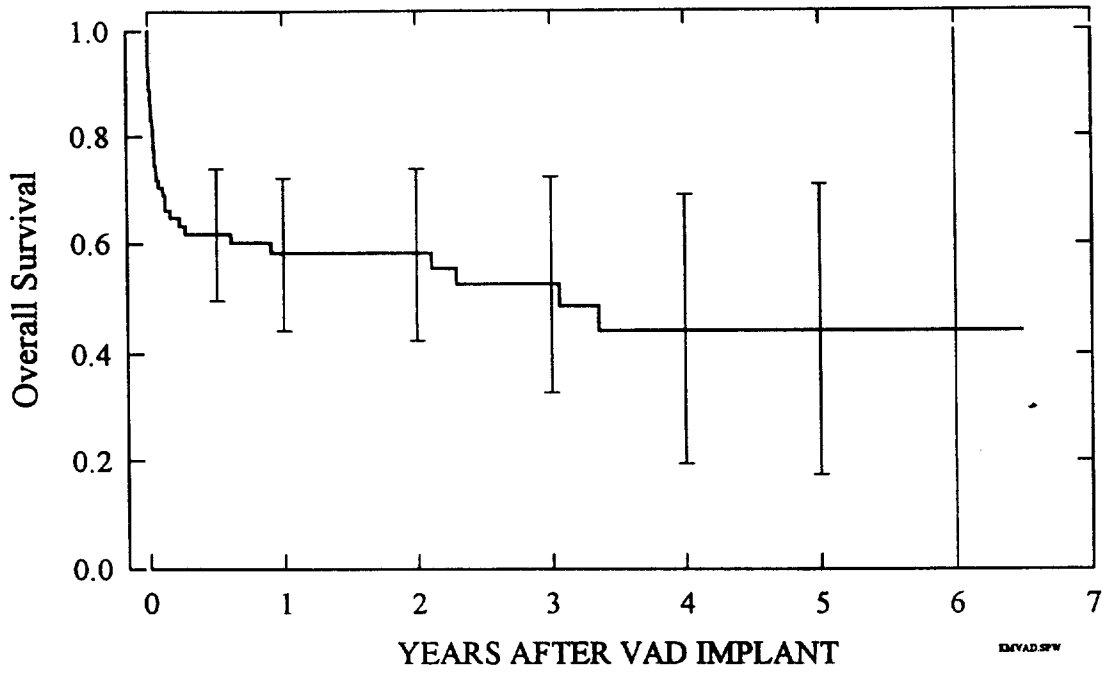
[1]Mann-Whitney U test

Figure XIII-1. Cumulative frequency distribution for days of VAD support, Cohort 1A (n = 71).



DAYS ON VAD[1]	GROUP		
	Not Transplanted (n = 22)	Transplanted (n = 49)	All Cohort 1A (n = 71)
Range	0.1 - 57	0.5 - 247	0.1 - 247
Median	6.8	23.2	15.7
Mean	13.0	45.1	35.1
SD	15.4	56.3	49.7
0 - 29	19 (86%)	27 (55%)	46 (65%)
30 - 59	3 (14%)	11 (22%)	14 (20%)
60 - 89	0	4 (8%)	4 (6%)
90 - 119	0	1 (2%)	1 (1%)
120 - 150	0	4 (8%)	4 (6%)
> 150	0	2 (4%)	2 (3%)

Figure XIII-2. Cumulative post-VAD implant survival probability (Kaplan-Meier plot) as of June 1, 1994 for all Cohort 1A patients (n = 71). Vertical lines are ± 95% confidence intervals.

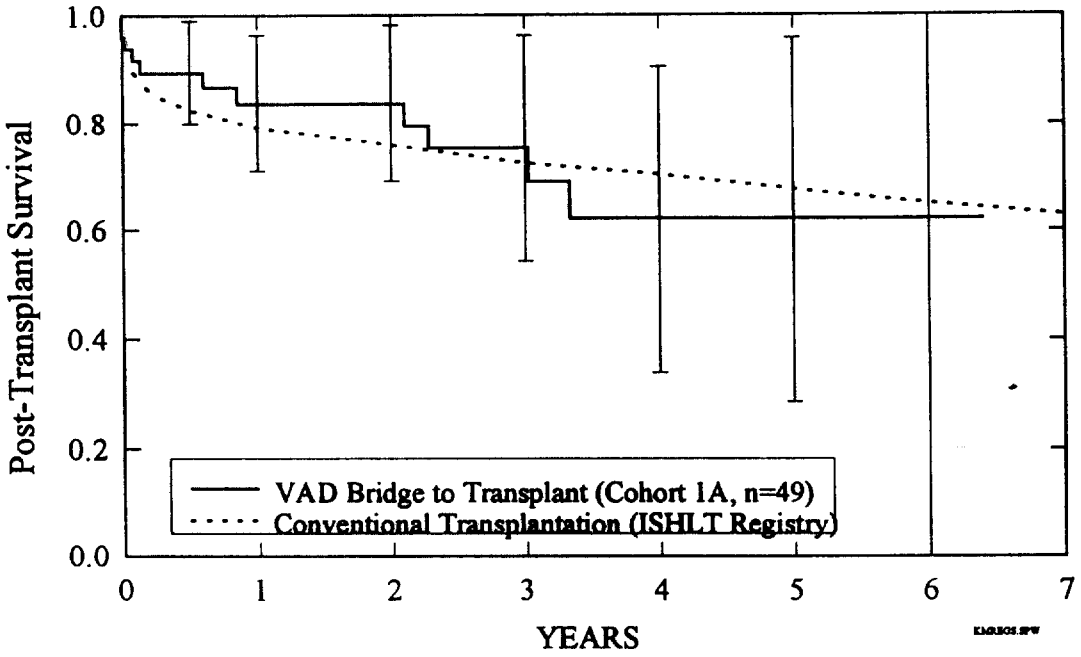


	INTERVAL, YEARS							
	0 - 0.5	0.5 - 1	1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6-7
# at start of interval	71	38	28	22	13	7	6	1
# died in interval	27	2	0	2	2	0	0	0
# died, cumulative[1]	27	29	29	31	33	33	33	33
# censored[2] in interval	6	8	6	7	4	1	5	1
# censored, cumulative	6	14	20	27	31	32	37	38
Probability of survival[3]	0.62	0.59	.59	0.53	0.45	0.45	0.45	0.45
± 95% confidence interval[4]	0.122	0.140	.158	0.198	0.248	0.268	0.655	--

Notes:

1. Number of deaths from beginning of study to end of interval.
2. Censored: Alive and have not yet reached the next interval as of the study cut-off date of 6/1/94.
3. Cumulative survival probability at end of interval.
4. At end of interval: $= 1.96 \times P_c \times SQRT((1-P_c)/N)$, P_c is cumulative survival probability, N is number of survivors, both at end of interval. From Peto et al.

Figure XIII-3. Cumulative post-transplant survival probability (Kaplan-Meier plot) as of June 1, 1994 for Cohort 1A patients who were transplanted (n = 49). Vertical lines are ±95% confidence intervals.



Kaplan-Meier post-transplant survival for Cohort 1A VAD patients was comparable to that for conventional heart transplantation as reported by the Registry of the International Society for Heart and Lung Transplantation (ISHLT) through 1992.†

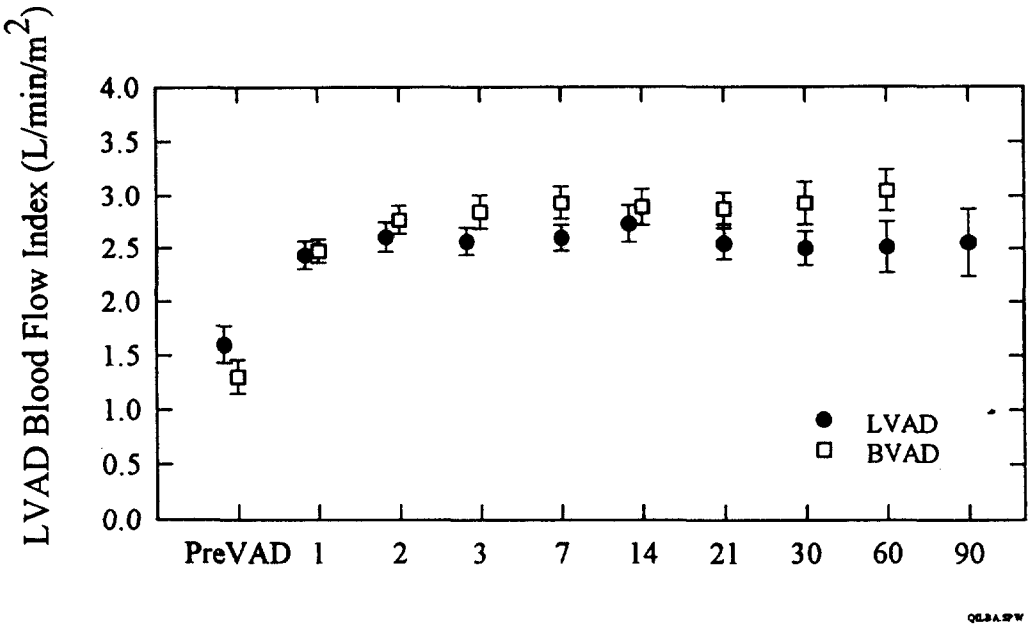
	INTERVAL, YEARS							
	0 - 0.5	0.5 - 1	1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7
# at start of interval	49	35	26	20	12	7	5	1
# died in interval	5	2	0	2	2	0	0	0
# died, cumulative[1]	5	7	7	9	11	11	11	11
# censored[2] in interval	9	7	6	6	3	2	4	1
# censored, cumulative	9	16	22	28	31	33	37	38
Probability of survival[3]	0.90	0.85	0.85	0.76	0.63	0.63	0.63	0.63
± 95% confidence interval[4]	0.095	0.127	0.145	0.210	0.284	0.336	0.752	-

Notes:

1. Number of deaths from beginning of study to end of interval.
2. Censored: Alive and have not yet reached the next interval as of the study cut-off date of 6/1/94.
3. Cumulative survival probability at end of interval.
4. At end of interval: $= 1.96 \times P_c \times SQRT((1-P_c)/N)$, P_c is cumulative survival probability, N is number of survivors, both at end of interval. From Peto et al.

† Kaye, M P. "The Registry of the International Society for Heart and Lung Transplantation: Tenth Official Report-1993." J Heart Lung Transplant 12(4):541-548, 1993.

Figure XIII-4. Cardiac index (CI) before, and LVAD flow index after VAD implantation for BVAD (n=49) and LVAD (n=22) patients, $\mu \pm 1.5$ SEM, L/min/m^2, Cohort 1A (n = 71). LVAD flow index measurement obtained by dividing VAD drive console display (L/min) by patient BSA (m^2).



LVAD Flow Index (L/min/m²)	DAYS ON VAD																			
	Pre-VAD[a]		1[b]		2[b]		3[b]		7[c]		14[c]		21[c]		30[c]		60[d]		90[d]	
	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD	BVAD	LVAD
Mean	1.3	1.6	2.5	2.4	2.8	2.6	2.8	2.6	2.9	2.6	2.9	2.7	2.9	2.5	2.9	2.5	3.1	2.5	-	2.6
Median	1.5	1.7	2.5	2.5	2.6	2.6	2.7	2.7	2.8	2.7	2.9	2.6	2.9	2.6	2.8	2.7	2.9	2.5	-	2.6
SD	.72	.50	.52	.40	.59	.42	.68	.41	.59	.36	.51	.51	.42	.36	.47	.37	.29	.46	-	.52
N	47	20	49	21	44	20	41	21	33	19	20	19	17	13	12	12	5	8	0	6
Min	0.0	0.0	1.2	1.8	2.0	1.9	2.0	1.9	1.9	2.0	2.1	2.1	2.1	1.9	2.1	1.8	2.8	1.9	-	1.9
Max	2.7	2.4	4.0	3.3	4.9	3.4	5.2	3.1	4.8	3.3	4.1	4.1	3.7	3.0	3.7	2.9	3.4	3.1	-	3.2
1.5 SEM	.16	.17	.11	.13	.13	.14	.16	.13	.15	.12	.17	.18	.15	.15	.20	.16	.19	.24	-	.32

Notes:

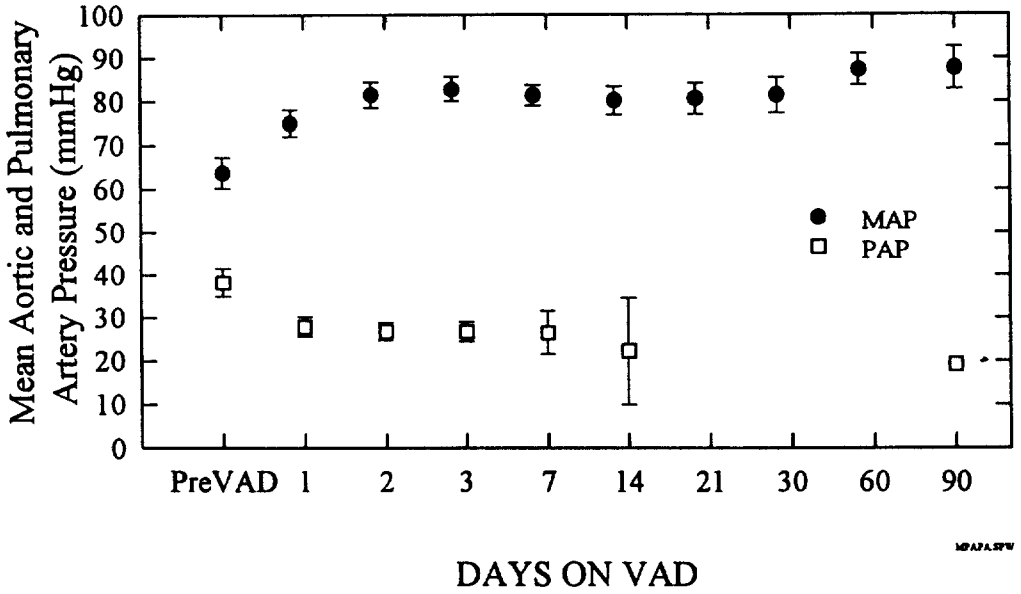
a. Last patient cardiac index obtained from PA catheter; generally within 24 hours prior to VAD implant.

b. Generally, at least 3 daily measurements; multiple daily measurements averaged over 24 hour period.

c. Average of 3 daily means for days n-1, n, and n+1.

d. Average of daily means over days n-5 to n+5.

Figure XIII-5. Mean aortic and pulmonary arterial pressures before and after VAD implantation, $\mu \pm 2.0$ SEM, mm Hg, Cohort 1A (n = 71). Aortic pressure measurements obtained from either arterial pressure line or pressure cuff, pulmonary pressure measurements obtained from PA catheter; lines pulled after patients stabilized.



Mean Arterial Pressure (mm Hg)	DAYS ON VAD																			
	Pre-VAD[a]		1[b]		2[b]		3[b]		7[c]		14[c]		21[c]		30[c]		60[d]		90[d]	
	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP	MAP	PAP
Mean	64	38	75	28	81	27	83	27	81	26	80	22	81	-	81	-	87	-	88	19
Median	63	36	75	28	80	27	82	26	80	25	80	26	78	-	81	-	86	-	86	19
SD	11.4	11.0	12.9	8.7	11.6	7.6	10.9	7.1	8.7	10.2	9.5	12.3	8.6	-	8.8	-	6.5	-	6.8	0.2
N	42	47	70	58	64	53	62	40	53	17	35	4	24	0	19	0	13	0	8	2
Min	35	21	37	7	52	6	65	11	62	8	58	5	57	-	63	-	76	-	80	19
Max	107	65	111	60	110	53	119	54	106	46	101	32	96	-	105	-	96	-	98	19
2.0 SEM	3.5	3.2	3.1	2.3	2.9	2.1	2.8	2.3	2.4	5.0	3.2	12.3	3.5	-	4.1	-	3.6	-	4.8	0.3

Notes:

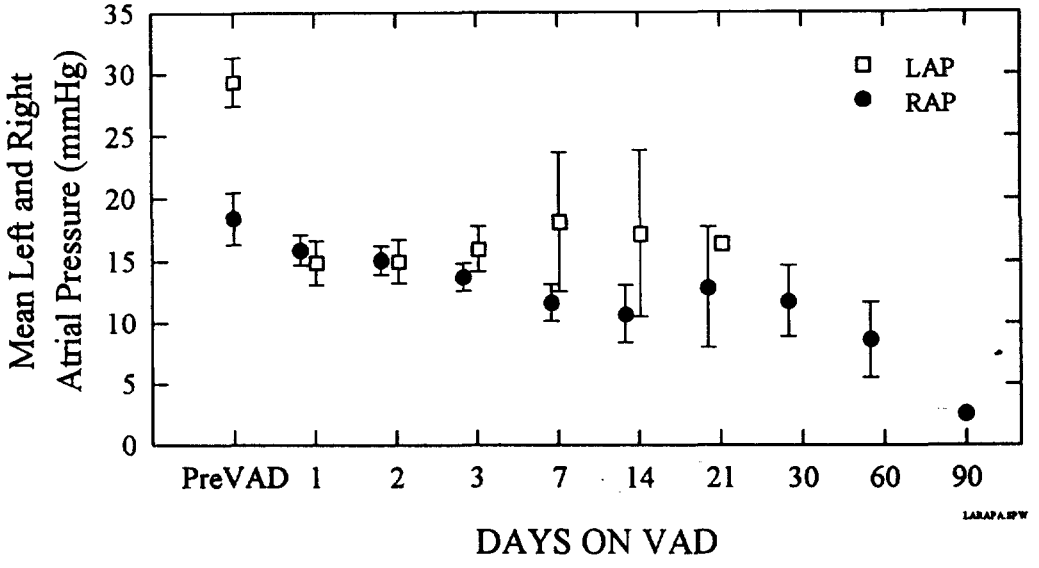
a. Last value measured generally within 24 hours prior to VAD implant.

b. Generally, at least 3 daily measurements; multiple daily measurements averaged over 24 hour period.

c. Average of 3 daily means for days n-1, n, and n+1.

d. Average of daily means over days n-5 to n+5.

Figure XIII-6. Mean left and right atrial pressures before and after VAD implantation, $\mu \pm 2.0$ SEM, mm Hg, Cohort 1A (n = 71). Left atrial measurements obtained from direct recordings or the pulmonary capillary wedge pressure, right atrial measurements obtained from CVP catheter; lines pulled after patients stabilized.



Mean Atrial Pressure (mm Hg)	DAYS ON VAD																			
	Pre-VAD[a]		1[b]		2[b]		3[b]		7[c]		14[c]		21[c]		30[c]		60[d]		90[d]	
	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP	LAP	RAP
Mean	29	18	15	16	15	15	16	14	18	12	17	11	16	13	--	12	--	9	--	3
Median	28	18	14	15	15	15	16	15	17	11	17	11	16	11	--	12	--	10	--	3
SD	7.6	7.7	6.1	5.0	5.2	4.5	4.9	4.0	10.3	4.4	4.7	4.6	0.0	6.9	--	2.0	--	2.7	--	0.0
N	61	56	47	66	35	59	29	54	14	34	2	15	1	8	0	2	0	3	0	1
Min	20	3	4	1	6	5	7	5	4	4	14	5	16	6	--	10	--	6	--	3
Max	50	32	37	29	29	25	27	20	43	23	21	19	16	28	--	13	--	11	--	3
2.0 SEM	1.9	2.1	1.8	1.2	1.8	1.2	1.8	1.1	5.5	1.5	6.7	2.4	0.0	4.9	--	2.9	--	3.1	--	0.0

Notes:

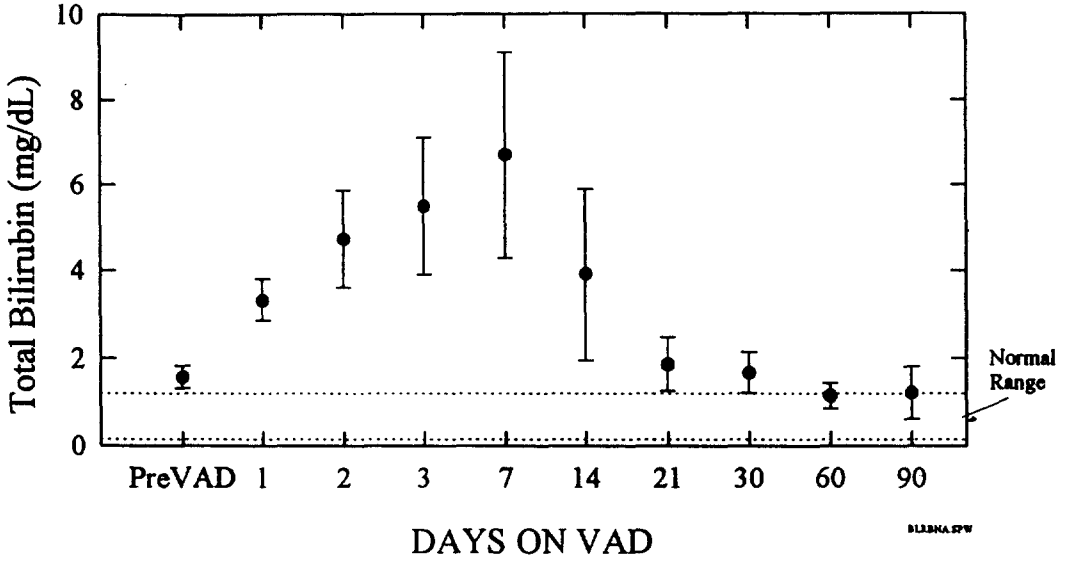
a. Last value measured generally within 24 hours prior to VAD implant.

b. Generally, at least 3 daily measurements; multiple daily measurements averaged over 24 hour period.

c. Average of 3 daily means for days n-1, n, and n+1.

d. Average of daily means over days n-5 to n+5.

Figure XIII-7. Total bilirubin before and after VAD implantation, $\mu \pm 2.0$ SEM, mg/dl, Cohort 1A (n=71).



Total Bilirubin (mg/dl)	DAYS ON VAD									
	Pre-VAD[a]	1[b]	2[b]	3[b]	7[c]	14[c]	21[c]	30[c]	60[d]	90[d]
Mean	1.57	3.32	4.73	5.50	6.69	3.91	1.86	1.67	1.14	1.21
Median	1.35	3.00	3.20	3.40	3.07	2.00	1.65	1.50	1.08	1.00
SD	1.01	1.73	3.97	5.40	8.53	5.50	1.37	0.87	0.41	0.52
N	64	54	50	46	50	31	20	14	8	3
Min	0.10	0.55	0.80	1.00	0.60	0.60	0.60	0.70	0.60	0.83
Max	4.20	7.60	19.25	25.50	29.35	28.00	6.97	3.98	1.93	1.80
2.0 SEM	0.25	0.47	1.12	1.59	2.41	1.97	0.61	0.47	0.29	0.60

Notes:

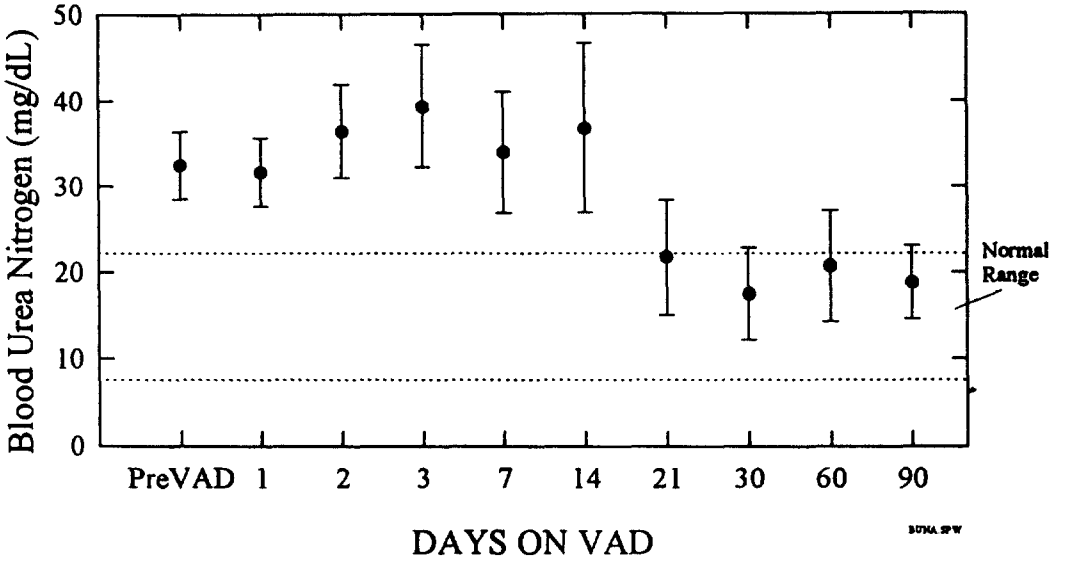
a. Last value measured; generally within 24 hours prior to VAD implant.

b. Generally, single daily measurement; multiple daily measurements averaged over 24 hour period.

c. Average of 3 daily means for days n-1, n, and n+1.

d. Average of daily means over days n-5 to n+5.

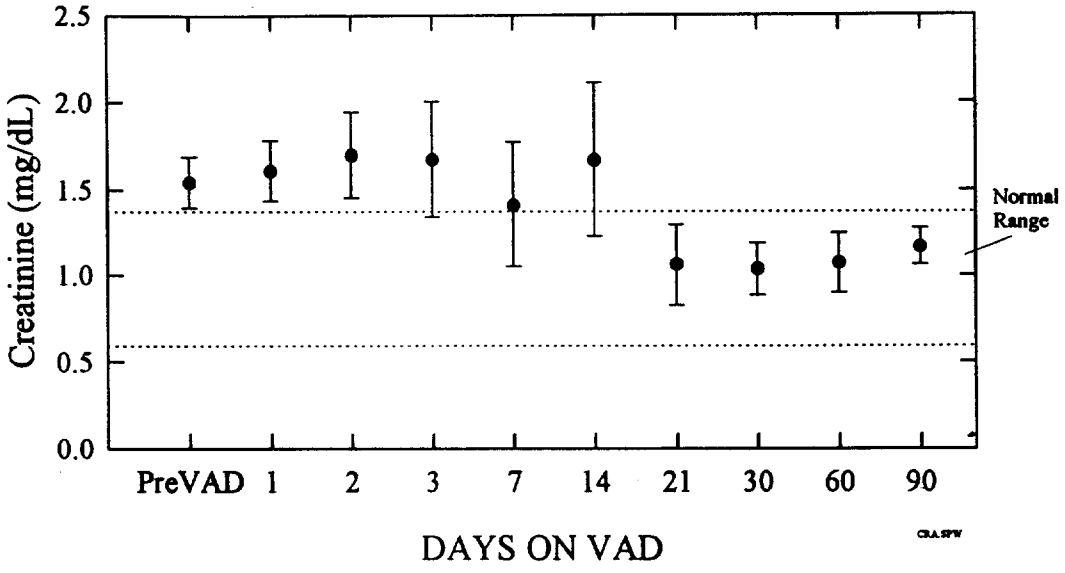
Figure XIII-8. Blood urea nitrogen before and after VAD implantation, $\mu \pm 2.0$ SEM, mg/dl, Cohort 1A (n=71).



Blood Urea Nitrogen (mg/dl)	DAYS ON VAD									
	Pre-VAD[a]	1[b]	2[b]	3[b]	7[c]	14[c]	21[c]	30[c]	60[d]	90[d]
Mean	32	32	36	39	34	37	22	17	21	19
Median	28	28	33	34	25	25	15	14	17	17
SD	16.4	16.2	21.5	26.5	25.2	30.0	17.3	12.5	11.1	5.6
N	69	65	61	55	50	37	27	22	12	7
Min	7	11	12	7	11	6	7	5	9	14
Max	83	78	134	160	115	120	90	65	44	30
2.0 SEM	4.0	4.0	5.5	7.2	7.1	9.9	6.7	5.3	6.4	4.2

Notes:
a. Last value measured; generally within 24 hours prior to VAD implant.
b. Generally, single daily measurement; multiple daily measurements averaged over 24 hour period.
c. Average of 3 daily means for days n-1, n, and n+1.
d. Average of daily means over days n-5 to n+5.

Figure XIII-9. Creatinine before and after VAD implantation, $\mu \pm 2.0$ SEM, mg/dl, Cohort 1A (n=71).



Creatinine (mg/dl)	DAYS ON VAD									
	Pre-VAD[a]	1[b]	2[b]	3[b]	7[c]	14[c]	21[c]	30[c]	60[d]	90[d]
Mean	1.5	1.6	1.7	1.7	1.4	1.7	1.1	1.0	1.1	1.2
Median	1.4	1.5	1.5	1.4	1.0	1.1	0.9	0.9	1.1	1.2
SD	0.61	0.70	0.96	1.23	1.29	1.34	0.61	0.36	0.30	0.14
N	69	65	61	56	51	37	27	22	12	7
Min	0.5	0.6	0.1	0.1	0.1	0.5	0.6	0.5	0.5	1.0
Max	3.5	3.8	5.2	6.5	6.5	5.5	3.2	2.3	1.5	1.4
2.0 SEM	0.15	0.17	0.24	0.33	0.36	0.44	0.24	0.15	0.17	0.11

Notes:

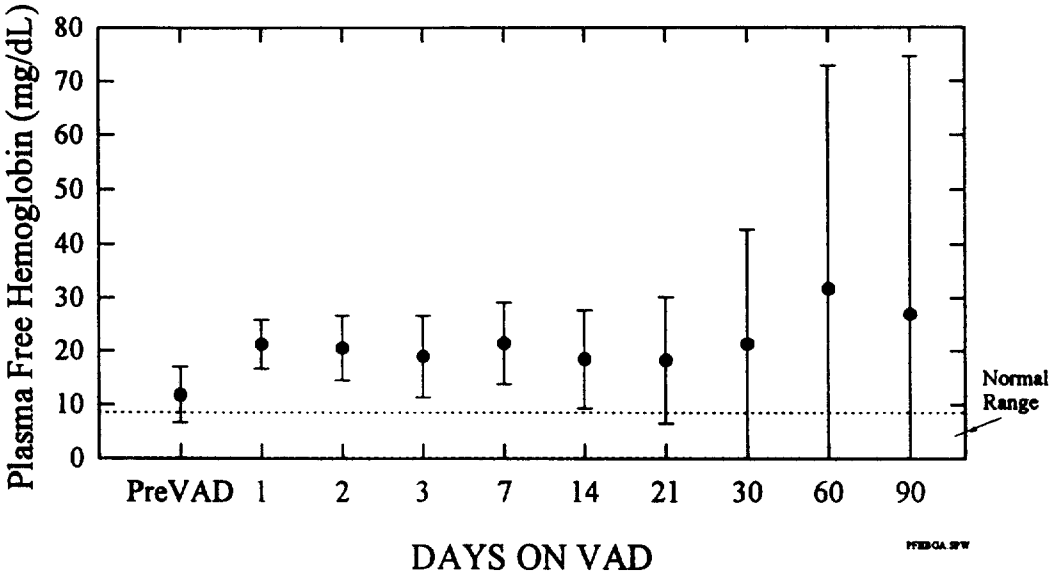
a. Last value measured; generally within 24 hours prior to VAD implant.

b. Generally, single daily measurement; multiple daily measurements averaged over 24 hour period.

c. Average of 3 daily means for days n-1, n, and n+1.

d. Average of daily means over days n-5 to n+5.

Figure XIII-10. Plasma free hemoglobin before and after VAD implantation, $\mu \pm 2.0$ SEM, mg/dl, Cohort 1A (n=71).



Plasma Free Hemo-globin (mg/dl)	DAYS ON VAD									
	Pre-VAD[a]	1[b]	2[b]	3[b]	7[c]	14[c]	21[c]	30[c]	60[d]	90[d]
Mean	11.73	21.18	20.50	18.92	21.36	18.44	18.31	21.33	31.69	26.98
Median	11.00	20.78	16.15	11.70	12.05	11.48	8.90	13.60	14.00	6.54
SD	11.26	13.81	18.31	20.96	21.63	17.27	21.32	30.14	54.38	41.20
N	19	36	37	30	32	14	13	8	7	3
Min	1.00	0.00	2.30	0.90	0.60	5.00	2.80	1.60	2.33	0.00
Max	46.2	61.8	102.0	92.0	116.3	55.1	72.0	94.5	154.0	74.4
2.0 SEM	5.17	4.60	6.02	7.65	7.65	9.23	11.83	21.31	41.10	47.57

Notes:
a. Last value measured; generally within 24 hours prior to VAD implant.
b. Generally, single daily measurement; multiple daily measurements averaged over 24 hour period.
c. Average of 3 daily means for days n-1, n, and n+1.
d. Average of daily means over days n-5 to n+5.

THORATEC® VENTRICULAR ASSIST DEVICE

DIRECTIONS FOR USE

Caution: Federal (USA) law restricts this device to sale by or on the order of a Physician

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(510) 841-1213
Facsimile: (510) 845-3935

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Table of Contents

THORATEC® VENTRICULAR ASSIST DEVICE
Directions for Use

SECTION I GENERAL INFORMATION

WARNING

A thorough understanding of the technical principles, clinical applications, and risks associated with ventricular support is necessary before using this product. Read this entire booklet, and the Dual Drive Console Directions for Use prior to attempting implantation. Completion of the Thoratec® VAD Training program is required prior to use of the Thoratec® Ventricular Assist Device (VAD) System.

1.0 DEVICE DESCRIPTION

The Thoratec® VAD System includes a ventricular assist device designed to support the circulation of blood in the pulmonary and/or systemic circulation when the natural heart, with the help of standard drug therapy and intraaortic balloon counterpulsation, is unable to maintain normal blood flows and pressures in those vascular beds. To accomplish this support, blood is shunted from the natural heart to the VAD, which then pumps pulsatile blood flow back to the body at normal arterial pressures.

The VAD System can be used in several configurations to provide for the circulation of blood in either or both the pulmonary or systemic vascular beds at physiological pressures and flows (see Figure 1). The system consists of three major components: a blood pump, cannulae, and a drive console. See Section 8.0 for a more detailed description of the system components.

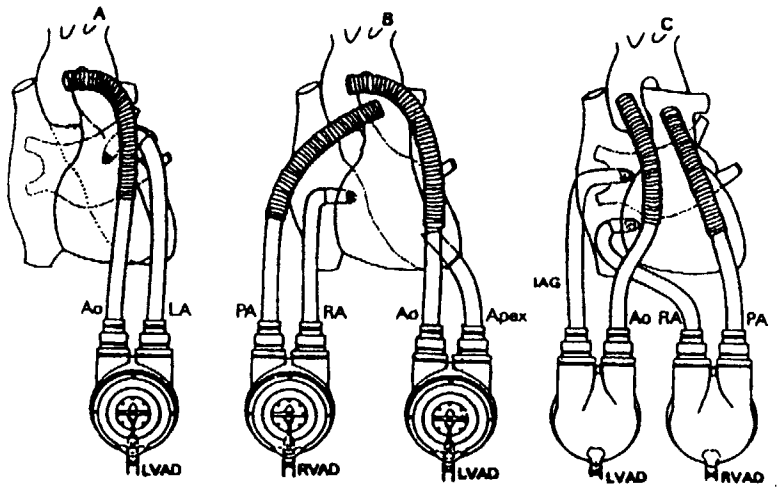


Figure 1. Thoratec® Ventricular Assist Device (VAD) and three cannulation approaches for univentricular left heart support (Panel A), and biventricular support (Panels B and C). Ao = aorta, LA = left atrial appendage, PA = pulmonary artery, RA = right atrium, Apex = left ventricular apex, IAG = cannula inserted via the interatrial groove and directed towards LA roof. Note that the VADs in Panel C are turned over and are on the sides of the chest that are opposite of those in Panel B. (Modified from Farrar DJ et al, New England Journal of Medicine 1988; 318: 333-340. Copyright 1988, Massachusetts Medical Society).

2.0 INDICATIONS FOR USE

The Thoratec® Ventricular Assist Device is intended as a bridge to cardiac transplantation for use in patients suffering from end-stage heart failure. The patient should meet all of the following criteria:

1. Candidate for cardiac transplantation.
2. Imminent risk of dying before donor heart procurement.
3. Dependence on, or incomplete response to, continued vasopressor support.

3.0 CONTRAINDICATIONS

None, other than contraindications to cardiac transplantation.

4.0 WARNINGS

4.1 Patient Population

VAD patients with prosthetic aortic valves may have increased risk of thromboembolism due to blood flow shunted away from the valve.

Patients with greater than 1.5+ aortic insufficiency should either not be considered a candidate for VAD support, or should be considered only after repair or replacement of the aortic valve.

Significant right-to-left shunting can occur in patients with a patent foramen ovale. Patency of the foramen ovale should be considered and corrected if necessary, prior to insertion of VADs.

Cannulas may be difficult to insert in patients with small hearts, or in patients with congenital abnormalities, or in patients with previous cardiac reconstructive surgery. There is no detailed data available at this time regarding this issue.

Patients with hepatic and/or renal dysfunction may require 2 to 3 weeks of VAD support for major organ function to recover.

Patients with elevated levels in the panel of reactive antibodies (PRA) may require extensive duration of VAD support in order to locate a donor heart. Patients should be excluded if the expectation of finding a donor heart is not reasonable.

4.2 Procedural Techniques

The VAD is provided sterile; caution must be taken in opening the package. Do not resterilize. Do not use if package is damaged.

Do not disassemble the VAD. Collet nuts and collets must be removed to attach cannulae to the VAD, and this can be performed by hand. Disassembly or attempts to loosen the cap ring, valve housing nuts, or any other component of the VAD may affect VAD function.

Do not use polar organic solvents, such as ketones, chlorinated hydrocarbons, and aromatic hydrocarbons, anywhere near the VAD. Such use has caused stress-cracking of the polysulfone and other damage to the VAD housing. These solvents include, but are not limited to, acetone, methyl ethyl ketone (MEK), methylene chloride, chloroform, trichloroethane, and benzene and its derivatives.

Do not use povidone-iodine (e.g., betadine) ointments, or other polyethylene glycol-based ointments in contact with the cannula for prophylactic care of the transdermal skin site. Such use over several months has caused cannula degradation at the end of the wire reinforced region. Povidone-iodine solution (not containing polyethylene glycol) is recommended.

5.0 PRECAUTIONS

5.1 Training of Personnel

Surgical, nursing, and perfusion staff responsible for the VAD program at each hospital should complete the Thoratec® VAD Training program.

5.2 Technique of VAD Placement

Use strict aseptic techniques during implantation and extreme care throughout VAD support to prevent infection.

The arterial graft on the arterial cannula must be preclotted before use.

Do not cut the tapered end of the atrial cannula.

The distal end of the arterial and ventricular cannulas can be trimmed, but at least 4 cm of nonwire reinforced polyurethane cannula are required for proper attachment to the VAD.

Do not allow tissue fluid or particulate matter to contaminate the inside of the cannulas, especially when passing the cannulas through the percutaneous exit tunnels.

The VAD valve housing has a very sharp edge designed to minimize seam thrombus. Do not dent or scratch the sharp edge, and be careful to avoid cutting yourself.

Do not allow blood or other fluids to contact the electrical fill switch connector on the VAD.

Do not initiate VAD pumping until the blood pump has been completely de-aired after connecting the cannulas.

If VAD cannulas are not properly inserted, suboptimal VAD blood flows may occur.

5.3 External Alarms

The VOLUME mode is the recommended control mode for most patients. This is the only mode where both audible and visual alarms on the Dual Drive Console (triggering on the absence of the VAD fill signal) are present if the VAD were to cease to operate due to adverse scenarios such as blockage of the pneumatic drive or cannulae. Any patient supported with the VAD drive console in the ASYNC or EXT SYNC modes must have the external alarm output on the drive console connected to the hospital nurse call system, or other similar external alarm system. This alarm output will trigger the external independent alarm after an 8 second absence of the VAD fill signal, thus alerting the user to check the VAD and drive console to determine that they are operating properly. This alarm is available in all control modes, but is redundant when using VOLUME mode since internal audible alarms are present in that mode.

5.4 Required System Backup

Each console contains two independent drive modules, and therefore contains adequate built-in back-up capability for univentricular support. For patients receiving biventricular support, a complete dual drive console must be available as a back-up to be used in the event of a failure of the primary console.

Personnel should be trained how to hand pump a VAD in the event of a drive console failure. If for any reason there is a drive console failure, blood flow can be maintained to the patient and stasis prevented in the blood pump by disconnecting the VAD airline tube from the drive console and connecting it to the hand bulb for the short period of time necessary to connect the back-up drive console. Squeeze the hand bulb about once per second to empty and fill the blood pump. Connect the back-up drive console as soon as possible. This procedure is for emergency use only.

5.5 Steps to Minimize the Risk of Thrombosis

At low beat rates there is an increased risk of thrombus formation in the VAD. Therefore it is recommended that the device be operated at rates above 40 bpm and with complete filling and ejection of the VAD blood pump in the VOLUME mode. Pneumatic drive ejection pressures of at least 100 mmHg above the patients systolic blood pressure are recommended for complete ejection. Complete VAD emptying can be verified by using a flashlight (see Section 10.7 for details). During weaning the patient from the VAD, and or during other conditions that result in low flow or beat rates below 40 bpm, continuous infusion of heparin for anticoagulation to achieve a partial thromboplastin time of 1.5 times control is recommended.

See Section 11.4 for anticoagulation regimen.

5.6 Interaction with Magnetic Resonance Imaging

This device contains ferro-magnetic metal components. Do not perform MRI imaging procedures on patients with the Thoratec® VAD.

6.0 ADVERSE EVENTS

Please refer to Table 1, Critical Adverse Events by Category, in Section 7.3 for more detailed information.

Based on the clinical study, the medical risks associated with the use of the VAD include the following critical adverse events (listed in order of decreasing frequency):

- Cardiovascular dysfunction
- Hepatic dysfunction
- Renal dysfunction
- Bleeding
- Hemolysis
- Infection
- Reoperation
- Death
- Thromboembolism

A variety of other adverse events were noted during the study including:

- Mechanical dysfunction
- Thrombocytopenia
- Neurological dysfunction
- Respiratory dysfunction
- Pleural effusions
- Pancreatitis

Note:

The need for reoperation may result from excessive bleeding, right ventricular failure requiring RVAD insertion, VAD inflow problems requiring cannula repositioning, etc.

Neurological dysfunction may result from pre-existing hypoxic brain injury (for example, from pre-VAD cardiac arrest or hypotension), or events during the VAD period such as cerebral hemorrhage, drug-related side effects, and cerebral hypoperfusion.

Embolism may result in stroke, pulmonary or other non-cerebral organ infarction, leg ischemia, or other vascular obstruction.

In addition, it is possible that the VAD will produce no significant hemodynamic improvement.

SECTION II PRIOR CLINICAL EVALUATION

7.0 CLINICAL BACKGROUND AND CONCERNS

7.1 Clinical Study Experience

Clinical study experience demonstrated that the Thoratec® Ventricular Assist Device System (VAD): 1) provided sustained improvement in hemodynamics and served as an effective bridge to transplantation; 2) did not negatively impact post-transplant survival rates.

The purpose of the study was to evaluate patients who had VADs placed prior to heart transplantation to maintain patient viability while waiting for a donor heart. Patients (ages 15-60 years) were selected who were awaiting heart transplantation and at imminent risk of death before a donor heart could be obtained. Qualifying patients [i.e., patients who met all of the study entrance criteria (Cohort 1A)] had received maximal conventional therapy, had pulmonary capillary wedge pressure ≥ 20 mmHg and either a cardiac index ≤ 1.8 L/min/m^2 or systolic pressure ≤ 90 mmHg or mean pressure ≤ 70 mmHg. Patients were excluded for total bilirubin ≥ 5 mg/dl or creatinine ≥ 4 mg/dl or irreversible end organ dysfunction. Seventy-one patients (54 males, 17 females) met all inclusion/exclusion criteria. The gender distribution (24% female) was consistent with the UNOS registry of patients awaiting cardiac transplantation (17.5% female). A retrospective control group (9 males, 1 female) met all the inclusion/exclusion criteria but were not treated with the ventricular assist system.

Results: Forty-nine of the 71 (65%) of the patients received biventricular (BVAD) support; 22 (35%) received only left ventricular (LVAD) support. Thirty-two patients required a total of 51 reoperations; 35 for bleeding; 16 for other reasons. Preoperative cardiac index (1.4 ± 0.7 ℓ/min/m^2 improved following VAD placement to an LVAD flow index of 2.5 ± 0.5 L/min/m^2 on post-VAD day 1 ($p < 0.001$) and remained within a clinically normal range thereafter. (At two weeks of VAD support, LVAD flow index averaged 2.8±0.5 L/min/m^2.) Median VAD support period was 16 days (mean: 35 days, maximum: 247 days). The median survival time from implant to follow-up cut-off date (June 1, 1994) was 223 days (mean: 503 days), with 38 current survivors. Median survival time was 10 days (mean: 14 days) in 10 control patients with 0 survivors. Of the 71 patients implanted with the device, 49 (69%) survived to receive a transplant compared to 0 of 10 control patients. Twenty-six of 55 (47%) patients implanted with the device survived at least 1 year post transplantation, and the other sixteen patients remained alive but had not yet reached the one-year period as of the study cut-off date (June 1, 1994). The Kaplan-Meier estimate of survival for the 49 transplanted patients was 84% at 1 year. Multivariate analysis identified two correlates of successful bridge to transplantation: low preoperative total bilirubin levels and absence of previous cardiac operations.

7.2 Criteria for BVAD Placement

Adequate right ventricular function is essential for the successful utilization of left ventricular assist devices, to provide sufficient blood flow through the pulmonary circulation to the left side of the heart. In situations where there are no accurate physiologic markers of right heart failure, an LVAD can be implanted first. Then a right ventricular assist device is used in addition to a left ventricular assist device (biventricular assist) when right heart failure prevents adequate function
of the LVAD, generally when the blood flow index is less than 2.0 ℓ/min/m^2 with a central venous pressure greater than 20 mmHg. Biventricular support is also indicated in patients with potentially lethal arrhythmias, or severe right ventricular infarction which could result in death during univentricular support. An RVAD may be considered at the time of LVAD implantation to obviate the need for a reoperation to implant the RVAD.

An isolated right ventricular assist device may also be suitable for patients with isolated right heart failure.

7.3 Adverse Events

Adverse events were collected for all 71 Cohort 1A patients enrolled in the study. The major risks associated with the use of ventricular assist devices are bleeding, infection, renal and hepatic dysfunction, hemolysis, thromboembolism, and reoperation.

Bleeding frequently occured after VAD implantation, and it can be due to surgical- and device-related reasons at the cannulation sites or arterial anastomoses, or it can occur due to coagulopathy. Fifty-one percent of the patients in this study had excessive post-operative bleeding, and reoperations to control bleeding were required in 31% of the patients, mostly in the first two post-operative days.

There was evidence that the VAD produces some hemolysis, with plasma free hemoglobin after 2 weeks of pumping averaging = 18 ± 9 mg/dL. Blood transfusions may be required for patients who have excessive bleeding or hemolysis.

Infection can also occur at the cannulation sites, around the monitoring lines, or in the blood, urinary tract, or respiratory tract. There was no apparent pattern of organisms or source. Infections (documented by at least one positive culture of blood, urine, sputum, or wound) occurred in 49% of patients, and sepsis was a cause of death in 7% of patients implanted with VADs.

Fifty-six percent of the patients in this study had evidence of hepatic dysfunction, and 54% showed renal dysfunction during VAD support. In some patients, 2 to 4 weeks of VAD support were required for recovery of these vital organs. Hemodialysis was required in 15% of VAD patients.

Thromboembolism can also occur from the VAD, cannulas, natural heart chambers, or arteries. Embolic stroke occured in 6 VAD patients (8% of the total). Continuous anticoagulation with heparin or warfarin is recommended.

The incidence of nine critical adverse events during the period of VAD support in the clinical trial is presented in Table 1. These events were recorded using all-encompassing definitions unique to this study, and therefore, comparisons with other devices and/or studies are not appropriate.

Table 1. Critical adverse events by category, while on VAD support, Cohort 1A, n=71.

EVENT CATEGORY	TOTAL		
	# Events	# Pts	% Pts
Cardiovascular dysfunction (e.g. any single event of hypo- or hypertension, arrhythmias, RV failure)	90	55	77%
Hepatic dysfunction (e.g. any single total bilirubin >3× high normal, cholecystitis)	40	40	56%
Renal dysfunction (e.g. dialysis, any single creatinine >1.5× high normal)	38	38	54%
Bleeding (e.g. excessive CT drainage, DIC, tamponade, hematuria)	54	36	51%
Hemolysis (e.g. any single plasma free hemoglobin >3× high normal after 24 hr)	36	36	51%
Infection (e.g. any positive culture, purulent discharge)	50	35	49%
Reoperation (for any cause - e.g. hemostasis, cannula reposition, tracheostomy, cholecystectomy)	51	32	45%
Death	22	22	31%
Thromboembolism (e.g. all autopsy evidence of any organ infarction; stroke, TIA)	27	20	28%

SECTION III HOW SUPPLIED

8.0 THORATEC® VAD SYSTEM COMPONENTS

8.1 Thoratec® VAD Blood Pump

The VAD blood pump is supplied sterile and non-pyrogenic for single-use only. Do not reuse or resterilize.

The central part of the system is the blood pump, which can be used as a left (LVAD), right (RVAD), or biventricular (BVAD) assist device. It has a rigid plastic case containing an elastomeric blood pumping sac, composed of Thoratec's polyurethane BPS-215M. The blood sac is compressed by air from a pneumatic drive console to eject blood from the sac. Mechanical valves, mounted in the inflow and outflow ports of the blood pump, control the direction of blood flow. The blood pump has an effective stroke volume of 65 ml and, depending on various conditions, will pump up to 6.5 l/min at a rate of 100 beats per minute.

8.2 Cannulae

The VAD cannulae are supplied sterile and non-pyrogenic for single-use only. Do not reuse or resterilize.

Each VAD blood pump is connected to the patient's heart and great vessels with cannulae. Cannulae can be inserted in the left or right atrium or placed in the left ventricular apex to provide inflow to the VAD blood pump. Blood is returned to the patient with an arterial cannula in the aorta or the pulmonary artery depending on whether the left or right ventricle is being assisted.

The VAD and connections to inflow and outflow cannulae are shown in Figure 2.

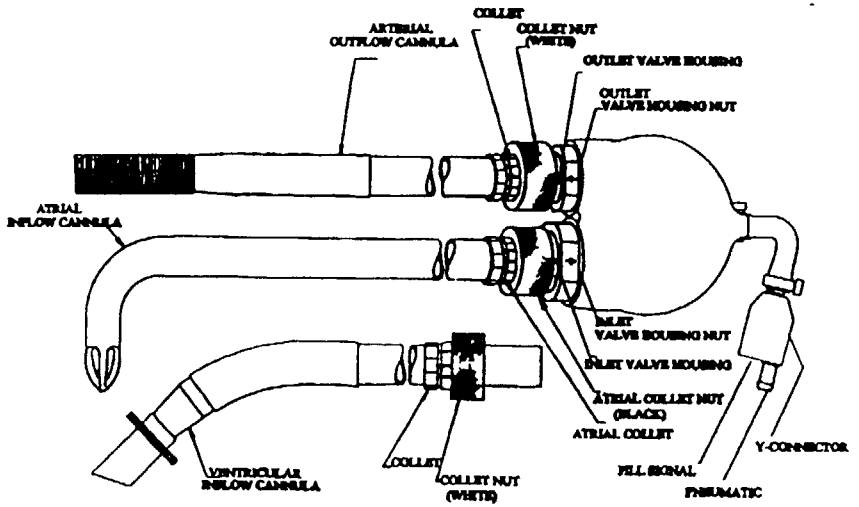


Figure 2. Thoratec® VAD shown connected to arterial and atrial cannulae. For apex cannulation, the ventricular inflow cannula and its collet and white collet nut are used in place of the atrial cannula and its collet and black collet nut.

Cannulae are provided in the following configurations (see also Appendix A):

Cannula Type	Cannula Tube		Tip		Cannula Shape
	Length	I.D.	Length	I.D.	
Atrial Inflow	25-30 cm	13 mm	2 cm cage	10 mm	90° bend
Ventricular Inflow	19-32 cm	16 mm	2-5 cm	12-15 mm	straight or curved
Arterial Outflow	15-20 cm	16 mm	30 cm polyester graft	14-18 mm	straight or curved

8.3 Pneumatic and Electrical Leads and Cannula Trocar

The pneumatic and electrical leads are provided sterile for single-use only. Do not reuse or resterilize.

The blood pump is connected to the drive console by flexible plastic pneumatic tubing for drive pressure and vacuum, and by an electrical cable for transmission of the signal from the fill switch from the pump to the driver.

The cannula trocar is provided non-sterile as a reusable instrument. It must be sterilized by steam autoclave before use.

8.4 Thoratec Dual Drive Console

Note: Refer to the Dual Drive Console Directions for Use for more information.

The drive console has two independent control modules and internal compressors to provide pressure and vacuum. The driver supplies pulses of pneumatic pressure to the blood pump to eject blood into the body. Each ejection period alternates with a filling period when blood, assisted by a slight vacuum, fills the VAD.

> PRECAUTION: Each console contains two independent drive modules, and therefore contains adequate built-in back-up capability for univentricular support. For patients receiving biventricular support, a complete dual drive console must be available as a back-up to be used in the event of a failure of the primary console.

Air pulses provided by the pneumatic driver can be controlled in three different modes: an asynchronous mode when a particular rate and percent systole is set by the user and the driver maintains those conditions indefinitely (fixed rate, variable stroke volume); a volume mode when ejection begins the instant complete filling occurs (variable rate, fixed stroke volume); and a synchronous mode when the driver, similar to an intraaortic balloon pump, provides counterpulsation using the patient's R-wave to end ejection (variable rate, variable stroke volume). The volume mode is used in most patients because the VAD flow responds automatically to changes in physiological conditions.

See Appendix A for a complete list of components and accessories with catalog order numbers.

9.0 RELIABILITY EVALUATION

The purpose of reliability testing is to obtain a reasonable estimate of how long a given device will perform, as intended, without failure. It is incumbent upon the attending physician, therefore, to be prepared for eventual device failures, and to anticipate the need for device replacement should patients require treatment for extended periods of time. See Section 10.9 for VAD replacement procedures.

Based on the *in-vitro* overall system reliability testing (through the study cut-off date), there is a 94% chance (using the lower 90% confidence intervals) that this device will be free of critical failures through 50 days of use, and a 65% chance that this device will be free of critical failures through one year of use.

SECTION IV IMPLANTATION PROCEDURE

10.0 CLINICAL PROCEDURES

Note: Refer to the following documents and videotapes for more information: a) Surgical Implantation Procedures videotape, b) the VAD Dual Drive Console videotape, c) the Dual Drive Console Directions for Use, and d) the Patient Management Manual.

10.1 Preparation of the VAD

Review VAD components and accessories to ensure that all components needed for the procedure are present.

Air from the VAD case chamber behind the blood pumping sac has already been evacuated during manufacturing, and normally no further action is required of the user. However, if necessary, more air can be removed with a 20 cc syringe and 22 gauge needle inserted through the small hole in the deairing port of the VAD case. Tilt the VAD to allow air to displace into the syringe and withdraw as much air as possible. Remove the syringe needle from the deairing port and from the sterile field.

Fill the VAD with a sterile heparinized albumin solution, 100 units of sodium heparin USP per 250 ml 5% albumin; typically 130 ml are needed to fill the VAD. Leave this solution in the VAD for 15 minutes before implantation (provides a passive protein coat on blood contacting surfaces). Use care to keep blood and other fluids from the electrical fill switch connector.

10.2 Preparation for Cannulation

Decide on length and type of inlet and outlet cannulas.

a. For most patients, the left ventricular apex is the preferred cannulation site for bridge to cardiac transplantation. Clinical experience has shown that higher blood flow levels can be achieved with this approach compared to atrial cannulation. Ventricular apex cannulation may also reduce the possibility of thrombosis in the natural left ventricle.

b. If left atrial cannulation is desired, the left atrial cannula can be inserted into either the left atrial appendage or via the interatrial groove. For the majority of patients, use the long atrial cannula (30 cm) for the left atrium and the short atrial cannula (25 cm) for the right atrium.

c. Position the cardiopulmonary bypass aortic perfusion cannula site so the 14 mm arterial graft on the VAD outflow cannula can be sutured to the right lateral border of the ascending aorta.

The LVAD is placed in a paracorporeal position as illustrated in Figure 3 (also see Figure 1). The percutaneous cannula sites will be approximately 4 cm apart below the costal margin. When LVAD inflow cannulation is from the LA appendage or the LV apex, the LVAD goes on the anterior abdominal wall to the left of the midline and the RVAD goes to the right of the midline, below the costal margin. If LVAD inflow cannulation is from the interatrial groove, then the LVAD is on the right and the RVAD is on the left of the midline. For LVAD placement, position both cannula exit incisions to the left of the midline to save space in the event a RVAD is needed.

Make short skin and fascial incisions to facilitate subsequent passage of the inflow and outflow cannulas (Figure 4). These openings must permit easy passage of the cannulas from the pericardial sac to the skin after the cannulas are attached to the heart and great vessels. Cannula tunnels should not be much larger than the outside diameter of the cannulas as this will allow fluid to collect and delay tissue adhesion to the velour cuff.

Plan for a length of 5 to 6 cm of cannula including 1 cm of velour cuff to be exposed on the patients abdomen for each cannula. For the arterial cannula, the entire polyester graft will remain in the chest. Cannula length determines the position of the VAD on the abdomen.

10.3 LVAD Inflow Cannulation

Blood flow to the LVAD can be provided by a ventricular inflow cannula in the left ventricular apex, or an atrial cannula in the left atrial appendage or the left atrium via the interatrial groove (Figure 1.). Cannulas can be crossclamped with smooth-jawed tubing clamps in the non-reinforced sections.

Cannulation of left ventricular apex

Caution: Use caution in attempting apical cannulation if the patient has sustained a recent infarct of this area of the heart.

Preplace six to twelve pledgeted double-armed 4-0 sutures around the apex. These should form a circle approximately 3-4 cm in diameter.

Coring of the ventricle can be accomplished by one of three methods: a) direct incision and cutting of the myocardium with scissors; b) use of a sharpened circular cutting tool, approximately 14 mm diameter, such as a cork borer; or 3) a commercial instrument such as that designed for placement of LV outflow conduits.

Once the apex is cored, inspect the ventricular chamber and remove any mural thrombus. Position cannula tips with beveled ends so that the long lip is against the ventricular septum.

When properly seated, pass each arm of the suture through the felt sewing cuff and tie it against the myocardium.

The free end is then brought out through the chest wall through the lateral of the two tunnels. This can be facilitated with the cannula trocar. It is suggested that the ventricular cannula be positioned in the heart before making the skin incisions. The exit site should be in a subcostal position so that the VAD will lie on the abdomen in the left upper quadrant. Intercostal lateral exit sites are not desirable because of cannula kinking and awkward VAD placement outside the body.

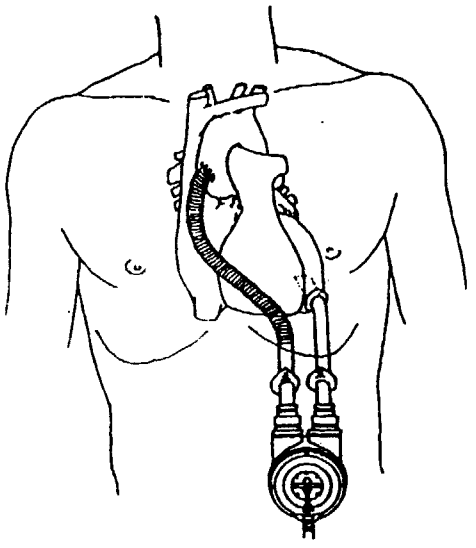


Figure 3. LVAD in a paracorporeal position, with cannulation from the left ventricular apex to ascending aorta.

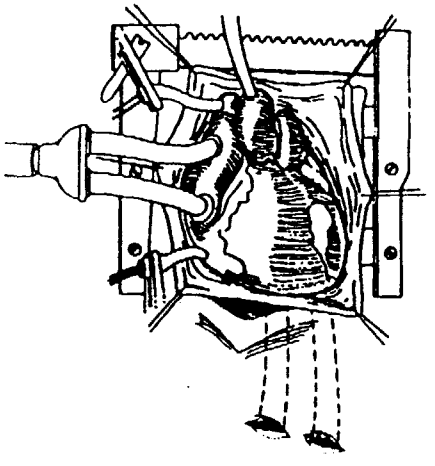


Figure 4. Percutaneous cannula exit sites below the left costal margin and to the left of the midline.

Cannulation of left atrial appendage

Caution: Suboptimal flow may occur if the cannula tip is obstructed in the atrium.
Caution: Do not trim the tapered end of the atrial cannula.

For atrial cannulation, it may be easier to pass the cannula through the lateral of the two subcostal tunnels before inserting it into the atrium. Retract the heart to the patient's right side, exposing the left atrial appendage (Figure 5). Place two 3-0 polypropylene purse string sutures at the base of the appendage. Begin and end each suture by passing it through a felt pledget. Leave the sutures long and pass them through 15 cm long rubber tube keepers.

Incise the left atrium and gradually dilate the opening with Hegar dilators. Insert the atrial cannula approximately 4 cm from the end of the tip (note: the single and double line markers are 5 and 6 cm from the tip, respectively). Tighten the rubber keepers and tie them over buttons. Secure the cannula by tying a tape ligature around each keeper and the cannula. Pass the cannula through the subcostal tunnel if this has not been done. The cannula trocar can facilitate this passage.

Cannulation of the left atrium via the interatrial groove

An alternate cannulation technique of the left atrium is via the interatrial groove. If the patient has a moderate to large left atrium with a friable or obliterated left atrial appendage, insert the inflow cannula into the left atrium along the interatrial groove between the right superior and inferior pulmonary veins (Figure 6). Do not insert the cannula directly into a pulmonary vein because of potential stasis thrombosis in the vein.

Use purestring sutures with keepers to suture the cannula in a similar fashion to that used for the left atrial appendage. With this cannula placement, the VAD will be positioned to the right of the midline and upside down with the fill switch side of the VAD against the abdomen as shown in Figure 1C.

10.4 VAD arterial outflow cannulation

Preclot arterial graft

Cut the tightly stretched graft to length.

Method A: Immerse it in blood (about 100 ml) mixed with 5 mg protamine and one ampule (5000 units) of topical thrombin. Massage into graft for 5 minutes until graft is sealed.

Method B:
a. Put 2 units (50 cc/unit) of cryoprecipitate in a kidney basin and massage into graft for 5 minutes.
b. Put 50 cc of thrombin (Parke-Davis, 1000 units/cc) in another kidney basin. Remove graft from cryoprecipitate and place in basin of thrombin and massage thrombin into graft for 3-4 minutes. A gel will form on the graft.
c. Flush out graft carefully with saline to remove any remaining thrombin. Carefully inspect interior of graft and remove all clumps of gel.

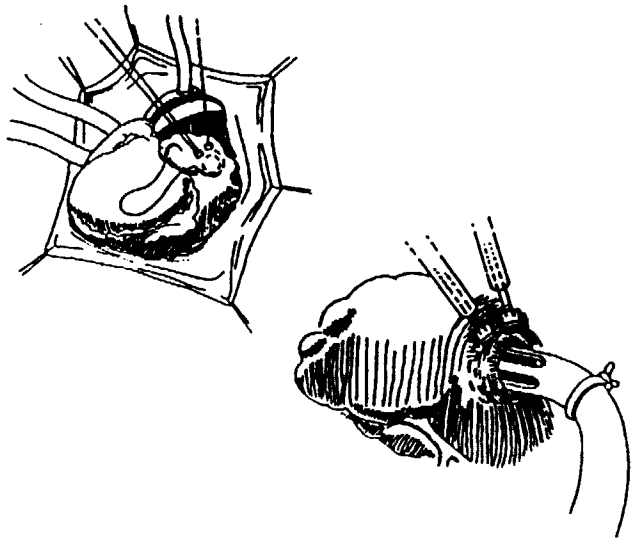


Figure 5. Cannulation of the left atrial appendage

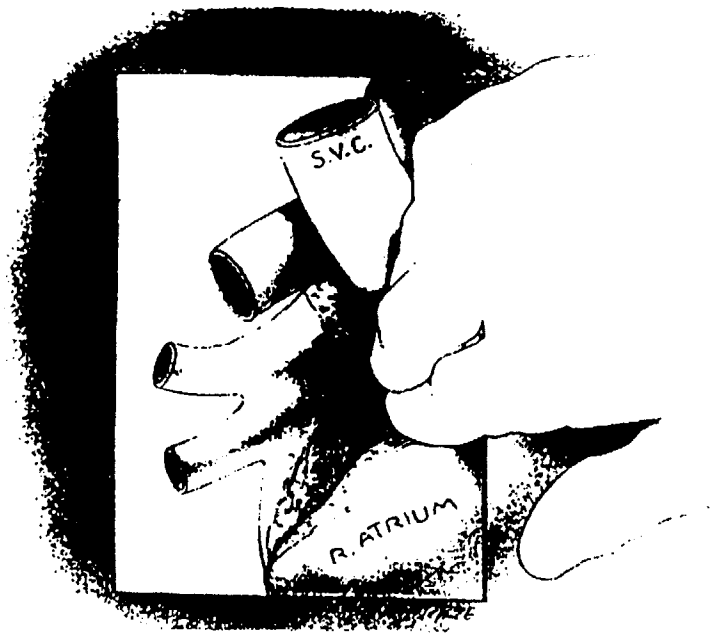


Figure 6. Cannulation site for the left atrium via the interatrial groove.

Aortic Anastomosis

Make sure the arterial graft is preclotted and cut (tightly stretched) to length. Apply an arterial tangential clamp (Beck) to the right lateral border of the ascending aorta, open the aorta, and anastomose the graft using double-armed 4-0 polypropylene suture (Figure 7). After completing the anastomosis, release the tangential clamp and deair the cannula. Apply a tubing clamp to the non wire-wound portion of the cannula. Cover the end with a rubber finger cut from a glove and pass the tube through the medial subcostal cannula tunnel. The cannula trocar can facilitate this passage.

If an atrial inflow cannula is in place, cut the distal polyurethane end of the arterial cannula to match the length of the flared atrial cannula. Do not cut the tapered end of the atrial cannula. If a ventricular inflow cannula is in place, trim the ventricular cannula and the arterial cannula as short as possible, but leave at least 4 cm of non wire-reinforced cannula for proper attachment to the VAD.

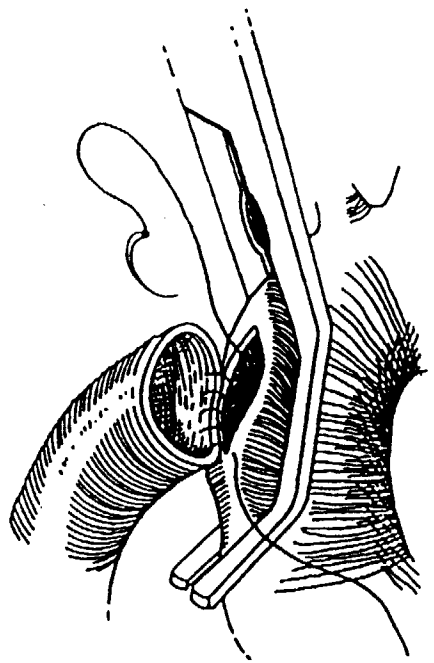


Figure 7. Aortic anastomosis.

10.5 Connect Cannulas to VAD and Eliminate Air

There are two sizes of cannula connectors. The smaller of the flared clamping ring collets and the white collet nuts are used for the arterial and ventricular cannulas. The atrial cannula requires the larger collet and the black collet nut. The standard VAD configuration is shipped with an arterial collet and white nut on the outflow port and with an atrial collet and black nut on the inflow port. If left ventricular cannulation is to be performed, remove the atrial collet and black nut and replace with the ventricular collet and white nut packaged with each ventricular cannula.

Keep both inflow and outflow cannulas clamped while securing cannulas on the VAD. Clamp the arterial graft near the aortic anastomosis. Carefully (to reduce bubbles) pour the heparinized albumin out of the VAD and refill with sterile saline. Remove the white arterial collet nut and the collet from the VAD and slide over the end of the VAD outflow cannula.

A deairing catheter can facilitate the removal of air in the VAD, which must be inserted prior to connecting the VAD arterial outflow cannula to the VAD. Nick the graft and insert a 5-7 F right angle angiography catheter filled with saline and connected to a 50 ml syringe and a three way stopcock. Place a 3-0 felt backed pursestring stitch at the graft nick and secure it with a tourniquet. Advance the catheter toward the VAD and out of the cannula and then through the outflow valve and into the VAD.

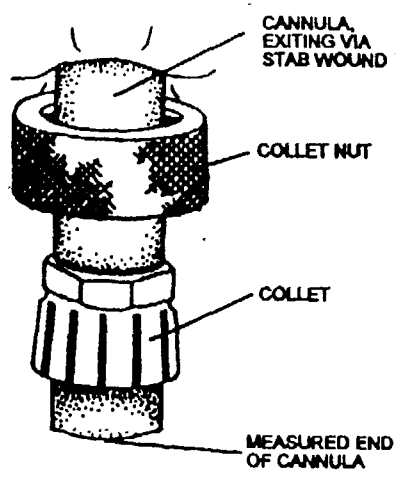
Position the arterial cannula on the VAD outflow port (Figure 8). Direction of blood flow is indicated by arrows on the valve housing nuts. Use gauze, if necessary, to work the cannula tip up the cone-shaped valve housing until the cannula edge is all the way into the connector groove.

> Caution: The valve housing has a very sharp edge designed to minimize seam thrombus. Do not dent or scratch this sharp edge and be careful to avoid cutting yourself.

When the cannula tube is fully seated on the valve housing, force the collet over the tube as far onto the VAD as possible. Using the back of a pair of forceps facilitates this process. Then tighten the nut firmly by hand.

Now attach the inflow cannula. Slide the correct inflow cannula collet and collet nut (black for atrial and white for ventricular apex) onto the inflow cannula. Hold the inflow cannula against the inlet connector of the VAD. Unclamp the arterial cannula and tilt the VAD so the uppermost portion of the inflow connector is high, thus eliminating air from the VAD. Then force the inflow cannula on the VAD cone shaped valve housing, again working it all the way into the connector groove. Slide the collet into place as far as possible and tighten the nut by hand.

Place the deairing catheter tip at the apex of VAD. Then unclamp the arterial cannula and withdraw air through the catheter. Make sure all air has been removed before withdrawing the catheter. Allow the small opening in the graft to bleed for the first few minutes of VAD pumping to evacuate any remaining bubbles, then seal by tying the previously placed pursestring suture.



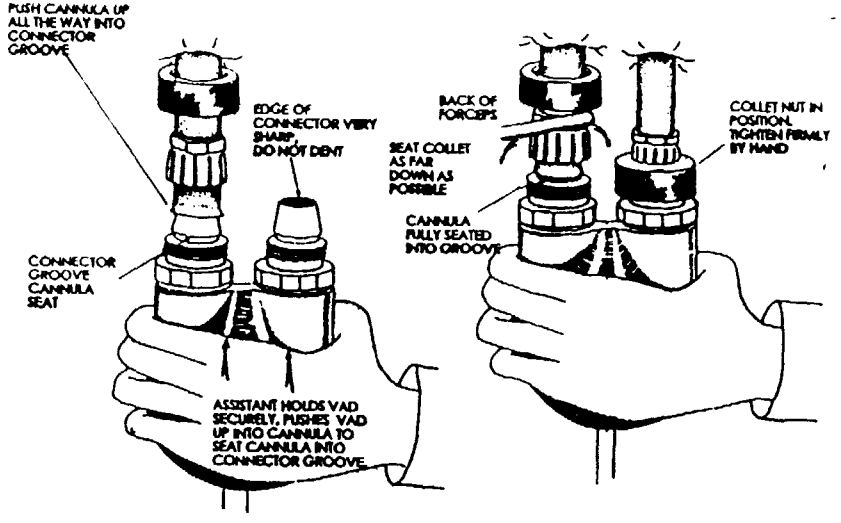


Figure 8. Cannula connections to VAD

10.6 Installation of RVAD

Use techniques similar to that for inserting the LVAD with atrial cannulation. Place the percutaneous cannula sites to the right of midline below the right costal margin. In those cases where the LVAD inflow is cannulated from the interatrial groove, the RVAD will be positioned to the left of midline. Use the short atrial cannula for most patients and place the atrial cannula in the body of the right atrium opposite the tricuspid valve rather than near the appendage. For the pulmonary arterial cannula, cut the arterial graft to length and preclot as for the LVAD. Cross the pulmonary arterial cannula over the aortic cannula before anastomosis to the upper surface of the main pulmonary artery. Connect the RVAD and deair as described for the LVAD.

10.7 Initiation of Pumping and Completion of procedure.

Refer to Dual Drive Console Directions for Use for more detailed procedures.

Connect the VAD pneumatic drive tube and electrical lead (align red dots on both halves of electrical connectors) to the VAD and pass the drive unit ends off the sterile field to the drive console technician.

Make sure the module selector valve on the inside of the console back door is correctly positioned in the middle position. Drive the VAD initially at a slow fixed rate (asynchronous fixed rate mode; 40 beats per minute, 20% systole), with a drive pressure initially set to about 100 to 110 mmHg and with vacuum at 0 to -4 mmHg. Check for VAD leaks at this time. Gradually increase eject pressure to over 200 mmHg with moderate levels of vacuum (i.e. -10 to -25 mmHg). When the VAD is filling and emptying regularly, the volume mode can be used.

> Caution: Applying excess vacuum with the chest open increases the risk of air embolism. If an atrial vent is to be removed or a direct left atrial pressure monitoring line is inserted, clamp the left atrial cannula before removing the vent or inserting the catheter, and keep the clamp in place until after the left atrial opening is sealed.

When the chest is closed, full vacuum (-25 to -40 mmHg) can be applied. It is recommended that the pneumatic drive pressure be set at least 100 mmHg above the systolic blood pressure (LVAD: 230 to 245 mmHg; RVAD: 140 to 160 mmHg) to completely empty the VAD with a systolic ejection time of 300 msec. Complete VAD emptying can be verified by shining a flashlight through the fill switch side of the pump housing and looking on the other side for a flash of light. Inadequate filling in the absence of cannula obstruction can often be treated with volume infusion.

After satisfactorily weaning the patient from cardiopulmonary bypass, administer the usual doses of protamine. Hold the sternum closed and check for adequate VAD filling and cannula positioning. Then completely close the sternum and skin with standard techniques.

10.8 Explantation of LVAD and RVAD

Administer intravenous antibiotics 1 hour before VAD removal.

Continue VAD pumping while the patient is moved from the intensive care unit to the operating room.

After induction of anesthesia, thoroughly prep chest, abdomen, VAD, and groin areas.

Wrap the external portion of the VAD and cannulas with sterile wraps, all of which will be passed as one package from the sterile field after removal.

Drape the patient and reopen the sternal incision.

> CAUTION: Use care to avoid cutting into the VAD cannulas and arterial grafts. Carefully remove any mediastinal clot and expose the cannulas.

If proceeding to heart transplantation, establish cardiopulmonary bypass and stop VAD pumping.

Clamp the inlet and outlet cannulas inside the chest and cut the cannulas near the inside chest wall.

Pull the VAD and attached cannulas through the chest wall as a single unit.

Remove remaining cannula sections from the heart and proceed with cardiac transplantation in the usual manner.

Patient management is conventional thereafter.

10.9 VAD Replacement Procedure

If for any reason a VAD requires replacement, the following procedure may be used (based on Lohmann DP, et al: Replacement of paracorporeal ventricular assist devices. Ann Thorac Surg 54:1226-1227, 1992). The cannulas are clamped and the VAD is removed from the cannula ends and a new VAD is attached.

Anesthetize, prep, and drape the patient in a sterile field.

Insert monitoring lines (arterial and Swan-Ganz) and make standby peripheral bypass available.

Anticoagulate the patient with heparin (1 mg/kg).

Apply povidone-iodine solution to all VAD surfaces, wipe dry with sterile towels, and respray with povidone-iodine. All surfaces should still be considered contaminated.

Insert lines for infusion of inotropic agents if required to provide some support during the period of VAD changeout.

Terminate VAD pumping. If the systolic blood pressure drops below 80 mmHg for more than 5 minutes, reinstitue VAD pumping and initiate cardiopulmonary bypass through groin vessels.

Clamp the VAD cannulas.

Remove the cannula connectors from the VAD and carefully remove the cannulas from the valve housing, taking care not to damage the ends that will be used on the replacement VAD.

Prepare a new VAD as in Section 10.1.

Connect the VAD to the inflow cannula. Slowly unclamp the cannula to allow the blood pump to fill with blood, then reclamp the cannula.

When the blood sac is nearly full of blood, partially connect the VAD to the outflow cannula.

Using a bulb syringe, squirt heparinized saline on the connectors while connecting the outflow cannula and VAD. If any air is present, the cannula must be removed and the step repeated until no air is in the VAD blood pump.

Once all air is eliminated from the system, VAD pumping can be initiated, and the patient can be weaned from inotropic support and/or cardiopulmonary bypass can be terminated.

SECTION V OTHER CONSIDERATIONS

11.0 PATIENT MANAGEMENT

11.1 Fluids, inotropic and vasoactive drugs

After implantation, the patient is returned to the cardiovascular intensive care unit. Fluids are given to maintain LVAD flow index at greater than 2.0 ℓ/min/m^2 with central venous pressure and left atrial pressure less than 20 mmHg. Some vasopressor and/or vasodilatory pharmacologic assistance can be used as required to adjust vasomotor tone. Patients with isolated LVAD support may require inotropic assistance of right ventricular function.

11.2 Infection Control

For prevention of infection, a broad spectrum cephalosporin should be used for antibiotic prophylaxis for the first 24 to 48 hours at a dosage of 1 to 3 gm/day, similar to that of other open-heart procedures. After this, organism-specific antibiotics are resumed as needed based on positive culture results. Early extubation and removal of monitoring lines and patient ambulation are to be encouraged. Rapid restoration of oral nutrition is attempted using tube feeding if necessary. Physical therapy and range of motion can begin after 24 hours. The patient can be moved to a chair and can use an exercise bicycle as soon as possible. Nursing measures to decrease infection include frequent hand washing, and strict aseptic technique during contact with invasive lines or during VAD cannula site dressing changes. Dressings around cannulae are changed twice daily for the first two days and then daily.

WARNING: Do not use Povidone-Iodine-ointment because of possible damage to cannulae (see Section 4.2); Povidone-Iodine solution is recommended.

11.3 Control of Bleeding

Bleeding is one of the more frequent adverse events in VAD patients. The chest tube output should be monitored every 30 to 60 minutes, and laboratory measurements of partial thromboplastin time, prothrombin time, fibrinogen and platelet count should be measured routinely. If bleeding is excessive, platelets can be given, and packed red blood cells and fresh frozen plasma are administered to correct for abnormalities in hematologic measurements. Re-exploration should be considered if chest tube output exceeds 200 ml/hour for 2 consecutive hours after clotting factors have been restored.

11.4 Anticoagulation Regimen :

Anticoagulation strategy is similar to that for patients with mechanical heart valves. Taking into consideration the patient's coagulation parameters, once the chest tube drainage falls to about 50 ml/hr for 2 to 3 hours (usually in the first or second postoperative day), anticoagulants should be considered to minimize the risk of thromboembolism. Two primary anticoagulation agents have been used in VAD patients: heparin and warfarin. Patients have been started on intravenous heparin on the first or second postoperative day at a dosage of approximately 10 units/kg/hr, gradually increasing to maintain the partial thromboplastin time at approximately 1.5 times control. As patients tolerate oral medication, they have been switched to oral warfarin in order to eliminate the intravenous line required for heparin. Warfarin has been administered similar to that for patients with mechanical heart valves to keep the International Normalized Ratio (INR) at 2.5 to 3.5. Low molecular weight dextran, aspirin, and persantine have also been used.

Appendix A

THORATEC® VAD SYSTEM COMPONENTS AND ACCESSORIES

	Description	Catalog No.
Clinical VAD	Ventricular Assist Device blood pump	14086-2550-000
Dual Drive Console	Model 2600, 110-120V/50-60 Hz	10025-2600-005
Clinical Arterial Outflow Cannula	Arterial Cannula, short, straight 15 cm long straight tube + 30 cm long graft (14mm ID)	14125-2559-000
	Arterial Cannula, short, curved 15 cm long curved tube + 30 cm long graft (14 mm ID)	14124-2561-000
	Arterial Cannula, long, straight 18 cm long straight tube + 30 cm long graft (14 mm ID)	14126-2558-000
	Arterial Cannula, long, curved 18 cm long curved tube + 30 cm long graft (14 mm ID)	14127-2560-000
	Arterial Cannula, long straight, 18 mm graft 18 cm long straight tube + 30 cm long graft (18 mm ID)	14812-2556-000
	Arterial Cannula, ex long, straight, 18 mm graft 20 cm long straight tube + 30 cm long graft (18 mm ID)	14813-2557-000
Clinical Atrial Inflow Cannula	Atrial cannula, short 25 cm long with right angle bend and 10 cm velour cuff	14120-2563-000
	Atrial cannula, long 30 cm long with right angle bend and 10 cm velour cuff	14121-2562-000
	Atrial cannula, long, with extra long velour 30 cm long with right angle bend and 13 cm velour cuff	14814-2575-000
Clinical Ventricular Inflow Cannula	Ventricular cannula with two side-holes 20 cm long straight tube + 5 cm long, 16 mm OD smooth tip (beveled, with 2 side-holes)	14111-2571-000
	Ventricular cannula, extra long, with two side-holes 25 cm long straight tube + 5 cm long, 16 mm OD smooth tip (beveled, with 2 side-holes)	14815-2568-000
	Ventricular cannula, blunt tip 27 cm long straight tube + 2.5 cm long, 16 mm OD velour-covered tip (blunt, no side-holes)	14114-2572-000
	Ventricular cannula, extra long, blunt tip 29 cm long straight tube + 2.5 cm long, 16 mm OD velour-covered tip (blunt, no side-holes)	14816-2569-000

Appendix A

THORATEC® VAD SYSTEM COMPONENTS AND ACCESSORIES

	Description	Catalog No.
	Ventricular cannula, short, curved 16 cm long curved tube + 3 cm long, 16 mm OD velour-covered tip (beveled, no side-holes)	14115-2565-000
	Ventricular cannula, long, curved 21 cm long curved tube + 3 cm long, 16 mm OD velour-covered tip (beveled, no side-holes)	14116-2564-000
	Ventricular cannula, long, large tip 28 cm long straight tube + 4 cm long, 19 mm OD smooth tip (beveled, no side-holes)	14819-2570-000
Accessories	Pneumatic Lead 8': Eight foot (2.4m) long pneumatic tube	14133-2580-000
	Pneumatic Lead 12': Twelve foot (3.5 m) long reinforced pneumatic tube, quick connects	14822-2579-000
	Electrical Lead 8': Eight foot (2.4 m) long fill switch cable	14144-2581-000
	Electrical Lead 12': Twelve foot (3.5 m) long fill switch cable	14823-2578-000
	Cannula Trocar	14451-2583-000
	External Alarm cable	14820-2584-000
	Hand Pumping Bulb	14148-2588-000
	Hand Pumping Bulb with Quick Connects	14787-2589-000
	External Pressure/Vacuum Connector set	10025-2585-000
Training	Clinical VAD Training Program	TRAIN-2599-VAD
	Dual Drive Console Directions for Use	14025
	Thoratec® VAD Console Operation with Illustrations	14803
	Dual Drive Console Quick Reference Card	14831
	Patient Management Manual	14577
	Videotape: Surgical Implantation Procedures	14804
	Videotape: VAD Dual Drive Console	14805
Training Devices	Animal VAD	14058-2552-000
	Animal Arterial Cannula 18 cm long straight tube + 15 cm long graft (18 mm ID)	13891-2590-000
	Animal Ventricular Cannula 31 cm long double bend tube + 4 cm long smooth tip (19 mm OD, beveled, no side-holes)	13910-2591-000
	Animal Atrial Cannula 30 cm long with right angle bend and 10 cm velour cuff	14049-2592-000